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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
B01J 8/06, B01L 3/14

A1

(11) International Publication Number: WO 96/33010

(43) International Publication Date: 24 October 1996 (24.10.96)

(21) International Application Number: PCT/US96/05339

(22) International Filing Date: 17 April 1996 (17.04.96)

(30) Priority Data:
08/422,869 17 April 1995 (17.04.95) US

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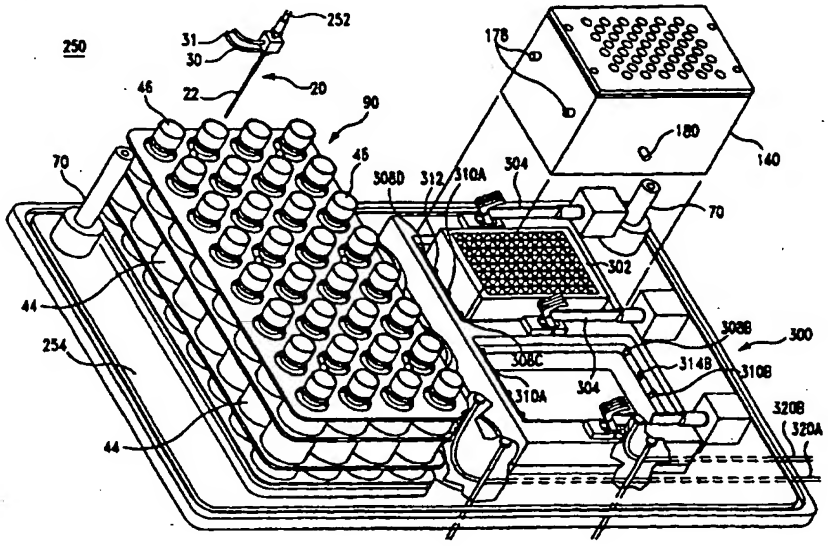
(81) Designated States: AU, CA, JP, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

(54) Title: METHODS AND APPARATUS FOR THE GENERATION OF CHEMICAL LIBRARIES



(57) Abstract

Method and apparatus for generation of chemical libraries are described. The apparatus includes a reaction block (140) which supports replaceable reaction chambers. Each reaction block is fitted with four sets of twelve reaction chambers. Reaction chambers are provided with s-shaped trap tubes which run into drain tubes. The reaction block is provided with gas lines and a septum seal such that gas pressurization empties the reaction chambers into the drain tubes. The drain tubes are arranged so as to mate directly with a standard 96 well microtiter plate for the collection of material. A docking station (300) secures registration of reaction blocks and introduces gases and liquids into the reaction blocks (140). An inert atmosphere is maintained in the reaction block by a top and an optional bottom seals. A needle (20) pipettes reagents from reagent containers (44) into reaction chambers. A container rack (90) keeps reagent containers securely in place.

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METHODS AND APPARATUS FOR THE GENERATION OF CHEMICAL LIBRARIES

FIELD OF THE INVENTION

The present invention relates generally to combinatorial synthesis, and more particularly to methods and apparatus for the generation of chemical libraries of known composition.

BACKGROUND

The relationship between structure and function of molecules is a fundamental issue in the study of biological and other chemistry-based systems. Structure-function relationships are important in understanding, for example, the function of enzymes, cellular communication, and cellular control and feedback mechanisms. Certain macromolecules are known to interact and bind to other molecules having a specific three-dimensional spatial and electronic distribution. Any macromolecule having such specificity can be considered a receptor, whether the macromolecule is an enzyme, a protein, a glycoprotein, an antibody, an oligonucleotide sequence of DNA, RNA or the like. The various molecules to which receptors bind are known as ligands.

Pharmaceutical drug discovery is one type of research that relies on the study of structure-function relationships. Much contemporary drug discovery involves discovering novel ligands with desirable patterns of specificity for biologically important receptors. Thus, the time necessary to bring new drugs to market could be greatly reduced through the use of methods and apparatus which allow rapid generation and screening of large numbers of ligands.

A common way to generate such ligands is to synthesize libraries of ligands on solid phase resins. Techniques for solid phase synthesis of peptides are described, for example, in Atherton and Sheppard, Solid

Phase Peptide Synthesis: A Practical Approach, IRL Press at Oxford University Press, Oxford, England, 1989. Techniques for solid phase synthesis of oligonucleotides are described in, for example, Gait, Oligonucleotide Synthesis: A Practical Approach, IRL Press at Oxford University Press, Oxford, England, 1984. Each of these references is incorporated herein by reference.

Techniques for solution and solid phase multiple component combinatorial array syntheses strategies include U.S. Patent Application No. 08/092,862 filed Jan. 13, 1994, which is assigned to the assignee of the present invention, and which is incorporated herein by reference. Other synthetic strategies that may be employed are described in, for example, Bunin and Ellman, "A General and Expedient Method for the Solid Phase Synthesis of 1,4-Benzodiazepine Derivatives," J. Amer. Chem. Soc. 114:10997-10998 (1992); Bunin *et al.*, "The Combinatorial Synthesis and Chemical and Biological Evaluation of a 1,4-Benzodiazepine Library," Proc. Natl. Acad. Sci. 91:4708-4712 (1994); U.S. Patent No. 5,288,514 entitled "Solid Phase and Combinatorial Synthesis of Benzodiazepine Compounds on a Solid Support," issued Feb. 22, 1994; and PCT Publication WI 94/08051, April 14 (1994), each of which is incorporated herein by reference.

Since the introduction of solid phase synthesis methods for peptides, oligonucleotides and other polynucleotides, new methods employing solid phase strategies have been developed that are capable of generating thousands, and in some cases even millions, of individual peptide or nucleic acid polymers using automated or manual techniques. These synthesis strategies, which generate families or libraries of compounds, are generally referred to as "combinatorial chemistry" or "combinatorial synthesis" strategies.

Combinatorial chemistry strategies can be a powerful tool for rapidly finding novel ligands to receptors of interest. To date, three general strategies for generating combinatorial libraries have emerged: "spatially-addressable," "split-bead," and "recombinant" strategies. These methods differ in one or more of the following aspects: reaction vessel design, polymer type and composition, control of physical variables such as time, temperature and atmosphere, isolation of products, solid-phase or solution-phase methods of assay (i.e., chemical analysis), simple or complex mixtures, and methods for finding or determining the structure of the individual library members.

Of these general strategies, several sub-strategies have been developed. One spatially-addressable strategy that has emerged involves the generation of peptide libraries on immobilized pins that fit the dimensions of standard, 96 well microtiter plates. See PCT patent publication Nos. 91/17271 and 91/19818, each of which is incorporated herein by reference. This method has been used to identify peptides which mimic discontinuous epitopes, Geysen et al., "Screening Chemically Synthesized Peptide Libraries for Biologically Relevant Molecules," Bioorg. Med. Chem. Lett. 3: 397-404 (1993), and to generate benzodiazepine libraries, U.S. Patent No. 5,288,514 entitled "Solid Phase and Combinatorial Synthesis of Benzodiazepine Compounds on a Solid Support," issued Feb. 22, 1994 and Bunin *et al.*, "The Combinatorial Synthesis and Chemical and Biological Evaluation of a 1,4-Benzodiazepine Library," Proc. Natl. Acad. Sci. 91:4708-4712 (1994). The structures of the individual library members can be determined by analyzing the pin location (in the microtiter plate) in conjunction with the sequence of reaction steps (called a "synthesis histogram") performed during the synthesis.

A second, related spatially-addressable strategy that has emerged involves solid-phase synthesis of polymers in individual reaction vessels, where the individual vessels are arranged into a single reaction unit. An illustrative example of such a reaction unit is a standard 96-well microtiter plate; the entire plate comprises the reaction unit and each well corresponds to a single reaction vessel. This approach is an extrapolation of traditional single-column solid-phase synthesis.

As is exemplified by the 96-well plate reaction unit, each reaction vessel is spatially defined by a two-dimensional matrix. Thus, the structures of individual library members can be determined by analyzing the sequence of reactions to which each well was subjected.

Another spatially-addressable strategy employs "teabags" (i.e., small, porous sacks) to hold synthesis resin. The reaction sequence to which each teabag is subject is recorded. This recorded reaction sequence determines the structure of the oligomer synthesized in each teabag. See for example, Lam et al., "A New Type of Synthetic Peptide Library for Identifying Ligand-Binding Activity," Nature 354:82-84 (1991), Houghton et al., "Generation and Use of Synthetic Peptide Combinatorial Libraries for Basic Research and Drug Discovery," Nature 354:84-86 (1991), and Jung et al., "Multiple Peptide Synthesis Methods and Their Applications," Agnew. Chem. Int. Ed. Engl. 31:367-383 (1992), each of which is incorporated herein by reference.

In another recent development, the techniques of photolithography, chemistry and biology have been combined to create large collections of oligomers and other compounds on the surface of a substrate. See U.S. Patent No. 5,143,854 and PCT patent publication Nos. 90/15070 and 92/10092, each of which is incorporated

herein by reference.

Recombinant methods for preparing collections of oligomers have also been developed. See PCT patent publication nos. 91/17271 and 91/19818, each of which is incorporated herein by reference. Using these methods, one can identify each oligomer in the library by determining the DNA coding sequences in a recombinant organism or phage. However, since the library members are generated in vivo (i.e., within the organism or phage), recombinant methods are limited to polymers whose synthesis can occur in the cell. Thus, these methods typically have been restricted to constructing peptide libraries.

A third general strategy that has emerged involves the use of "split-bead" combinatorial synthesis strategies. See Furka et al., "General Methods for Rapid Synthesis of Multicomponent Peptide Mixtures," Int. J. Pept. Protein Res. 37: 487-493, (1991) which is incorporated herein by reference. In this method, beads are apportioned into smaller groups. These smaller groups (called "aliquots") each contain a number of beads that is evenly divisible into the total number of beads. Each aliquot exposed to a monomer, and the beads are pooled together again. The beads are mixed, reapportioned into aliquots, and then exposed to a second monomer. The process is repeated until the desired library is generated.

A technique for synthesizing labelled combinatorial chemistry libraries is described in co-pending application serial number 08/383,776, entitled "Methods and Apparatus for Synthesizing Labeled Combinatorial Chemical Libraries," filed February 2, 1995, assigned to the assignee of the present invention, and incorporated herein by reference. In a preferred embodiment of that invention, each synthesized compound is associated with a unique identifier tag. The identifier tag relates a

signal to a detector upon excitation with electromagnetic radiation.

To aid in the generation of combinatorial chemical libraries, scientific instruments have been produced which automatically perform many or all of the steps required to generate such libraries. An example of an automated combinatorial chemical library synthesizer is the Model 396 MPS fully automated multiple peptide synthesizer, manufactured by Advanced ChemTech, Inc. ("ACT") of Louisville, KY.

The Model 396 MPS is capable of generating up to 96 different peptides or other small molecules in a single run. The syntheses occur simultaneously, with one amino acid being added to each growing polypeptide chain before addition of the next successive amino acid to any polypeptide chain. Thus, each growing polypeptide chain contains the same number of amino acid residues at the end of each synthesis cycle.

The syntheses occur in an ACT proprietary plastic reaction block having 96 reaction chambers. While the ACT reaction blocks work for their intended purpose, they possess several shortcomings.

First, ACT reaction blocks are machined from a single piece of plastic. Thus, they require extremely intricate machining, and are quite expensive to manufacture. Furthermore, since ACT reaction blocks are in the form of a single unit, should a portion of a block become damaged or contaminated in some way, the entire reaction block would have to be discarded; there is no way to replace individual portions of an ACT block.

An additional drawback of the plastic ACT reaction blocks is that they cannot be efficiently heated or cooled to aid in chemical reactions that may require such heating or cooling.

Certain processes and chemistries require that the chemical reagents (which may be reactants, solvents, or

reactants dissolved in solvents) be kept under an inert or anhydrous atmosphere to prevent reactive groups from reacting with molecular oxygen, water vapor, or other agents commonly found in air. Examples of atmosphere or moisture sensitive chemistries include peptide chemistry, nucleic acid chemistry, organometallic, heterocyclic, and chemistries commonly used to construct combinatorial chemistry libraries. Accordingly, such reagents must be stored and used under an anhydrous or inert atmosphere, such as one of argon, nitrogen, or other gases or mixtures of gases. Typically, containers of such reagents (and containers in which reactions using these reagents take place) are sealed from outside air by a gas impermeable septum. Reagents may be removed from or introduced into a septum sealed container via a non-coring pipetting needle that pierces the septum.

The composition of the septum depends on the chemistry involved, but common materials include thermoplastic rubber (TPR), natural rubber, teflon (typically used as a lining), and EPDM.

While the ACT reaction block can maintain an inert atmosphere when locked in place on the work station of the Model 396 MPS, there is no way to maintain an inert atmosphere once an ACT reaction block is removed from the work station. Thus, the reaction block must remain docked at the work station during the entire synthesis cycle. Since many reactants require several hours to react, this represents significant down time for the Model 396 MPS pipetting station, as it remains idle during the reaction period.

Additionally, creating an effective seal that maintains an inert atmosphere within the ACT reaction block is difficult due to the design of the block. To create such a seal, a top plate fitted with a rubber gasket is clamped onto the reaction chamber using six set screws. The screws are hand tightened to create the

seal. The top of the block is machined such that a raised rim or bead separates the 96 reaction chambers into four sections of 24 reaction chambers each. Thus, individual chambers within a group of 24 are not sealed with a raised bead but rather sealed with a flat junction between the septa and the flat top of the machined polymeric reaction block. This design provides an inferior seal and allows solvent from the reaction chambers to cross contaminate reaction chambers within each group of 24 by creeping along the underside of the septa material or alternatively, by creeping along the gas passages machined into the top of the reaction block. Proper adjustment of the screws to distribute pressure evenly across each of the four sections (to create an effective seal) requires careful manipulation and cannot always be accomplished successfully.

A poorly formed seal can also create a problem with reagent cross-contamination. If the gasket does not seal evenly around each reaction chamber, reagents may seep from one reaction vessel into another.

While the ACT reaction block includes 96 reaction chambers, the compounds generated in the ACT reaction block cannot be directly transferred into a standard 96-well microtiter plate because the distance between the outlets of the reaction chambers is too great. For each reaction chamber to have the volume needed to perform reactions, the 96-reaction chamber ACT reaction block must necessarily be too large to mate with a standard 96-well microtiter plate. When reactions are complete, the user must transfer the contents of the reaction chambers into an array of 96 flat bottom glass vials supported in a plastic frame. The user must then manually pipette fluid from the glass vials into a microtiter plate for further analysis. This arrangement presents several disadvantages. First, the glass vials must be cleaned between uses, which increases the chance for

contamination. Furthermore, the labor intensive nature of the transfer increases a chance for error. Finally, this process cannot easily be automated.

The reagent delivery system of the Model 396 MPS also suffers limitations. While the septum-sealed reagent containers from which the reactants are drawn can be sealed under an inert or anhydrous atmosphere, the volume of reagent removed is not replaced with an equivalent or greater volume of inert gas. As reagents are withdrawn from the reagent containers, a partial vacuum is generated within the containers. If the pressure difference between the inside of the container and the external atmosphere is great enough, outside air may seep into the container through needle holes previously made in the septum.

The Model 396 MPS also employs a capacitance detector that can determine the fluid surface level in a reagent bottle. During operation of the Model 396 MPS, fluid is removed from reagent bottles by inserting a pipetting needle just below the fluid surface level such that reagent directly at the reagent-atmosphere interface is withdrawn. While this operation permits only the very tip of a pipetting needle to be contaminated, this operation may also result in the withdrawal of reagent that has been exposed to outside air.

Finally, the MPS detector described above can only operate if polar reagents are used. Thus, the Model 396 MPS may not be compatible with chemistries that utilize non-polar reagents.

Accordingly, there remains a need in the art for a relatively inexpensive, easy to manufacture reaction block having replaceable parts. There also remains a need in the art for a reaction block that can be efficiently heated and cooled, that can be moved from place to place while maintaining an inert atmosphere, and that can mate directly with a standard 96 well microtiter

plate. An additional need that remains in the art is for a reaction block that easily and effectively seals each reaction chamber, and that reduces cross-contamination of reagents between reaction chambers. There also remains a need in the art for a reaction block that can be manipulated robotically.

There also remains a need in the art for a pipetting work station that can be operated to withdraw reagent from the bottom of a reagent bottle, away from the reagent-atmosphere interface, and that can be used with non-polar reagents.

There remains a further need in the art for a holder for septa sealed reagent bottles which prevents the movement of these bottles caused by friction between a pipetting needle and the septa seals.

SUMMARY

The preferred embodiments meet these needs by providing a reaction block which uses replaceable reaction chambers supported in the block. Each reaction block is fitted with four sets of 12 reaction chambers, and has fittings that facilitate robotic manipulation.

The reaction chambers are preferably fitted with a frit. An s-shaped trap tube snaps into a fitting on the bottom of each reaction chamber. The trap tube runs into a drain tube.

The reaction block is fitted with gas (preferably N_2) lines and a septum seal such that gas pressurization empties the reaction chambers into the drain tubes. The drain tubes are arranged so as to mate directly with a standard 96 well microtiter plate for the collection of material.

The reaction blocks preferably have high thermal stability and are preferably fitted with gas or liquid lines for heating or cooling.

A docking station provides for secure registration

of the reaction blocks, and provides for introduction of gases and liquids into the reaction blocks. An inert atmosphere in the reaction block is maintained by a top and (optional) bottom seal. A synthesis support may be introduced as a slurry or powder through the fastened septa with a suitable septa-piercing needle assembly. Alternatively, a synthesis support may be introduced into each reaction chamber as a slurry or powder with the top removed and the top then fastened after addition. A needle pipettes reagents from an array of reagent containers into the reaction chambers, and maintains the inert atmosphere. A locking reagent container rack keeps the containers securely in place.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a plan view of a pipetting work station according to a preferred embodiment.

Figure 2 is a side and top view of a reaction chamber according to a preferred embodiment.

Figure 3 is a side cross-sectional view of the reaction chamber shown in **Figure 2** further including a trap tube and drain tube.

Figure 4 is an isometric view of a reaction block and its associated hardware according to a preferred embodiment.

Figure 5 is a top view of the reaction block shown in **Figure 4**.

Figure 6 is a side cross-sectional view of the reaction block shown in **Figure 4**.

Figure 7 is a side cross-sectional view of the reaction block shown in **Figure 4** including a removable bottom seal.

Figure 8 is a side cross-sectional view of the reaction block shown in **Figure 4** including a microtiter plate.

Figure 9 is a bottom view of the reaction block shown in **Figure 4**.

Figure 10 is a bottom plan view of the reaction block shown in **Figure 4**.

Figure 11 is a top view of a locking reagent container rack according to a preferred embodiment.

Figure 12 is a side view of the locking reagent container rack shown in **Figure 11**.

Figure 13 is a top view of a docking station according to a preferred embodiment.

Figure 14 is a cross sectional view of a connector in the docking station shown in **Figure 13**, inserted into a port in the reaction block shown in **Figure 4**.

Figure 15 is a cross sectional view of a connector in the docking station shown in **Figure 13**, inserted

into a port having a open valve in the reaction block shown in **Figure 4**.

Figure 16 is a cross sectional view of a connector in the docking station shown in **Figure 13**, inserted into a port having a closed valve in the reaction block shown in **Figure 4**.

DETAILED DESCRIPTION

The structure and function of the preferred embodiments can best be understood by reference to the drawings. The reader will note that the same reference numerals appear in multiple figures. Where this is the case, the numerals refer to the same or corresponding structure in those figures.

GENERAL OPERATION

Figure 1 is a plan view showing a portion of an automated pipetting work station **250** as may be used in a preferred embodiment. Automated pipetting work station **250** may be a TECAN 5032 automated pipetting work station (manufactured by TECAN AG, Feldbachstrasse 80, CH-8634 Hombrechtikon, Switzerland) with one or more pipetting arms **252**. Pipetting arm **252** attaches to needle assembly **20**, which is preferably a coaxial needle assembly of the type disclosed in concurrently filed application serial no. 08/423,142 (attorney docket no. 8140-010) entitled "Pipetting Needle for Fluid Transfer Under Inert Atmosphere Operations," assigned to the assignee of the present invention and incorporated herein by reference. Coaxial needle assembly **20** includes a needle **22**, a gas inlet port **30**, and may also include an electrical connection **31**. Work station **250** may also include pipetting needle rinse stations **70**, preferably of the type disclosed in concurrently filed application serial no. 08/423,141 (attorney docket no. 8140-011) entitled "Pipetting Needle Rinse Station" assigned to the assignee of the present invention, and incorporated herein by

reference.

A locking reagent container rack **90** holds several containers **44** of reagents sealed from the outside air with septum seals **46**. Rack **90** is preferably placed on the left side of work station deck **254**. On the right side of work station deck **254** is a docking station **300** for receiving two reaction blocks **140**. Each reaction block **140** contains an array of 48 reaction chambers **110** (see, e.g., **Figure 4**). A standard 96 well microtiter plate **302** may be mounted below reaction block **140** when product is to be removed from reaction chambers **110**.

REACTION CHAMBER

Referring now to **Figure 2**, a reaction chamber **110** according to a preferred embodiment is shown. Reaction chamber **110** is preferably made of an injection molded or extruded polymer such as polypropylene, although polyethylene, teflon, glass, or any other inert material able to withstand the temperature, pressure, and chemical environment to which reaction chamber **110** is exposed could also be used. Reaction chamber **110** preferably also has an internal volume of approximately 2 ml.

Reaction chamber **110** includes a generally cylindrical body portion **112** of a first diameter, and a generally cylindrical lower body portion **114** that is coaxial with and of a smaller diameter than body portion **112**. Body portion **112** is connected to generally cylindrical lower body portion **114** by frustum, or tapered section **116**. Body portion **112** has a top opening **118** which preferably has a rounded top surface **120** to facilitate sealing against a septum. Body **112** has a gas input port **122** located below top surface **120**. Gas input port **122** is positioned such that it will be located above the bottom of waste basin **160** of reaction block **140** (See **Figures 4** and **5**). As will be discussed below, this positioning will prevent possible cross-contamination of chemicals by blocking a direct flow path

from port to port or from port to septum.

Reaction chamber **110** preferably also includes a keying protrusion **128**. Keying protrusion **128** prevents reaction chamber **110** from being inserted into reaction block **140** unless it is in a predetermined orientation. This feature will be discussed further below.

Lower portion **114** of reaction chamber **110** can receive a frit **124**, which preferably supports a quantity of a synthesis support such as solid phase resin (not shown). Frit **124** is preferably a 70 micron polyethylene frit, although other types of frits such as sintered glass, sintered metals, and sintered ceramics may be used depending on the type of chemistry to be performed.

Frit **124** is preferably press fit into lower portion **114**. Lower portion **114** has a smaller diameter than that of body **112** to allow insertion of frit **124** into lower portion **114** without damaging the inside surfaces of body **112**. Lower portion **114** preferably also includes an annular bead **126** to retain frit **124** when it is pressed into place.

Reaction chamber **110** also includes a funnel shaped portion **130** immediately below lower portion **114**, and below frit **124**. Funnel shaped portion **130** allows full area exposure to the underside of frit **124**, to enhance the draining of liquids from reaction chamber **110**.

Immediately below funnel portion **130** is a generally cylindrical drain tube **132**. Drain tube **132** is coaxial with and of smaller diameter than lower body portion **114**. Drain tube **132** includes an annular sealing bead **134** to create a seal against the outside of S-shaped trap tube **136** (see **Figure 3**). This seal may be strengthened by welding (or otherwise fixing) S-shaped trap tube **136** to annular sealing bead **134**.

The purpose of trap tube **136** is to prevent the loss of liquids from reaction chamber **110** (when reaction chamber **110** is not pressurized) by bringing the level of

an outlet for liquid above the normal liquid level of reaction chamber **110**. Trap tube **136** connects to a drain tube **138**. When reaction chamber **110** is pressurized, liquid flows through trap tube **136** and out drain tube **138**. As will be discussed below, drain tube **138** will be positioned so as to deposit liquid into a well of a standard 96-well microtiter plate.

Trap tube **136** and drain tube **138** are preferably made of an injection molded or extruded polymer such as polypropylene, although polyethylene, teflon, or any other inert material able to withstand the temperature, pressure, and chemical environment to which trap tube **136** and drain tube **138** are exposed could also be used.

REACTION BLOCK

Referring now to **Figure 4**, an isometric view of a reaction block **140** (and its associated hardware) according to a preferred embodiment is shown. Reaction block **140** is preferably machined out of 6061 aluminum (which is easily machinable and has good corrosion resistance) and then anodized for additional corrosion protection. Reaction block **140** could also be hard coat anodized followed by teflon impregnation. Additionally reaction block **140** could be machined or molded from any suitable metal, engineering plastics, filled plastics, crystalline plastics, ceramics, machinable ceramics, or any other material that can withstand the temperature, pressure, and chemical environment to which reaction block **140** will be exposed. If non-metallic materials are used, product reaction could be enhanced by the application of microwaves. If materials transparent to ultraviolet (UV) light are used, product could be cleaved from the synthesis support using UV light, and without the application of an acid or base.

Each end of reaction block **140** is preferably fitted with two pins **178** to facilitate handling by a robotic gripper (not shown). Each side of reaction block **140** is

preferably fitted with one pin **180** to facilitate securing reaction block **140** onto docking station **300**. Robotic manipulation of reaction block **140** makes automation of the entire synthesis process possible. For example, reagents could be introduced into reaction chambers **110** when reaction block **140** is locked onto docking station **300** of pipetting work station **250**. Reaction block **140** could then be moved to a separate docking station **300**, vortexing shaker table, heating or cooling chamber, or any other location or device (not shown) useful in synthesis or the collection of material.

In a preferred embodiment, two types of reaction blocks capable of mating directly with a 96 well microtiter plate are contemplated: the 48 reaction chamber **110** (and drain tube **138**) positions of a first type of (or "A") block are offset from the 48 reaction chamber and drain tube positions of a second type of (or "B") block such that a type "A" and a type "B" block can fill every position in a standard 96 well microtiter plate. The ability to deposit material directly into a 96-well microtiter plate eliminates the possible contamination and human error problems discussed above with respect to the ACT reaction block.

Reaction block **140** may be color coded for ease of identification, may have identification numbers **320** machined into or printed on the sides, and may also have a bar code **322** printed on the side for identification by machine.

Referring now to **Figure 5**, top portion **142** of reaction block **140** is shown. Top portion **142** preferably has an array of circular openings **144** arranged in a staggered grid. In a preferred embodiment, reaction block **140** has 48 circular openings **144**. Openings **144** also preferably include a keying notch **145** (see **Figure 4**) which cooperates with keying protrusion **128** on reaction chamber **110** and requires reaction chamber **110**

to be in a predetermined orientation when inserted into opening **144**.

The 48 openings **144** are divided into four chambers **146A** through **146D** of twelve openings **144** each. The chambers **146A-D** are separated from each other by a plurality of raised beads **148**, which are preferably machined into top portion **142**.

Top portion **142** also includes four gas inlet ports **150A** through **150D**. Gas flows from gas inlet ports **150A-D**, into gas inlet chambers **152A** through **152D**, respectively (which are defined by raised sealing beads **148**). Gas then flows out through chamber exit ports **154A** through **154D**, respectively, and into chambers **146A** through **146D**, respectively. Gas flow to each chamber **146** can be individually controlled. For example, chambers **146A** and **146C** can be pressurized, without pressurizing chambers **146B** and **146D**.

When reaction chambers **110** are inserted and locked into place in openings **144**, the top portions **120** of reaction chambers **110** are in approximately the same plane as the tops of raised sealing beads **148**.

Top surfaces **120** of reaction chambers **110** and raised sealing beads **148** are sealed by a sheet of septum material **153** (**See Figure 4**). Septum **153** is preferably manufactured from 1/10" thermoplastic rubber (TPR) sheet. Septum **153** is retained by a septum retainer plate **155**, which is preferably fastened with six captive screw-type fasteners **156** which attach to openings **157**. Fasteners **156** pass through openings **159** in septum **153**, and screw into machined fastener openings **158**.

Reaction block **140** may be sealed from underneath with a bottom seal **220**. An o-ring or quad ring **221** (see **Figure 7**) may be used to ensure a gas-tight seal. Bottom seal **220** may include a one-way valve **222** to allow pressure regulation. Bottom seal **220** is preferably fitted to reaction block **140** with screw-type fasteners

224. As can be seen in **Figure 4**, fasteners **224** pass through openings **226** in plate **155**, through openings **228** in septum **153**, through openings **228** in reaction block **140**, and into openings **232** in bottom seal **220**. Bottom seal **220** permits a desired atmosphere or pressure to be maintained within reaction block **140**, allowing reaction block **140** to be moved from location to location (such as to a separate shaker table, not shown) without loss of such atmosphere or pressure. This can be especially useful in chemistries requiring long periods of time for reactions to take place. In these situations, such reactions can take place away from the pipetting work station, allowing the pipetting work station to be used for other purposes.

In a preferred embodiment, septum retainer plate **155** is machined from 6061 aluminum and anodized. However, retainer plate **155** could also be machined or molded from engineering plastics, ceramics, or any other material that can withstand the temperature, pressure, and chemical environment to which retainer plate **155** will be exposed.

Plate **155** is also preferably machined with 48 openings **162** positionally matched with openings **144** of reaction block **140** (and thus with openings **118** of reaction chambers **110**) to accurately control the compression of the septum **153** between the tops **120** of reaction chambers **110**, and plate **155**.

Chambers **146 A through D** include recessed waste basins **160 A through D**, respectively, which are machined into top portion **142** below the level of chamber exit ports **154A - D**. This prevents a back flow of fluids from waste basins **160A - D** into chamber exit ports **154A - D**.

As discussed above, reaction chambers **110** and openings **144** are preferably "keyed" with keying protrusions **128** and keying notches **145**, respectively.

This prevents reaction chambers **110** from being inserted fully into openings **144** unless the reaction chambers are in a predetermined proper orientation. In a preferred embodiment, reaction chambers **110** are oriented such that gas inlet ports **122** face away from chamber exit ports **154A - D**. This prevents back flow of liquids from reaction chambers **110** into the chamber exit ports **154A - D**. In addition, gas inlet ports **122** of reaction chambers **110** are oriented such that a back flow of liquid from one reaction chamber **110** is prevented from spilling directly into the gas inlet port **122** of an adjoining reaction chamber **110**.

Referring now to **Figure 6**, a side cross-sectional view of reaction block **140** is shown. Reaction chambers **110** are held in place by machined annular steps **170** (which define openings **171**), and machined annular beads **172**. S-shaped trap tube **136** and drain tube **138** are held in place by a friction fit against walls **174** and openings **176** (See **Figures 9 and 10**).

Steps **177** are machined into the bottom of reaction block **140** to allow reaction block **140** to mate directly with a standard 96-well microtiter plate **302** (see, e.g., **Figures 1** and **8**). Steps **177** also allow mating and sealing with bottom seal **220** (see **Figures 4** and **7**).

Referring now to **Figures 9 and 10**, plan and bottom views of reaction block **140** are shown. The underside of reaction block **140** includes a generally planar surface **190** which includes a plurality of openings **171** and **176**, discussed above. Openings **176** include a relatively larger portion **192**, which accommodates drain tube **138**, and a relatively smaller portion **194**, which accommodates s-shaped trap tube **136**.

The underside of reaction block **140** also includes four gas ports **196A** through **196D** located on bottom surface **198**. Ports **196A-D** connect to gas inlet ports **150A-D** (See **Figure 5**), respectively, through machined

tunnels (not shown) in reaction block **140**.

Also included on bottom surface **198** is a gas inlet port **200** which connects to a gas outlet port **201** via a machined tunnel (not shown). This allows pressure on the underside of reaction block **140** to be independently controlled when it is sealed by bottom seal **220** (see **Figures 4** and **7**).

Bottom surface **198** also includes two gas or liquid ports **202A** and **202B**. The interior of reaction block **140** is preferably machined to include passages (not shown) in which heating or cooling gas or liquid can flow if desired. Gas or liquid can enter port **202A** and exit through port **202B**, or vice versa. If reaction block **140** is made of material having high thermal stability or thermal mass such as 6061 aluminum, this arrangement allows reaction block **140** to be quickly and efficiently heated or cooled for chemistries that require such heating or cooling.

Ports **196A-D**, **200** and **202** may also serve as guide pin holes to position reaction block **140** properly on docking station **300** (see **Figures 1** and **13**).

Finally, a bar magnet **204** may be mounted flush with surface **198**. Bar magnet **204** serves to activate magnetic reed switch **314** mounted in docking station **300** (see **Figure 13**). As will be discussed below, one or more reed switches prevent the operation of work station **250** unless one or more reaction blocks **140** are properly in place.

DOCKING STATION

Referring now to **Figures 1, 13** and **14**, a docking station **300** according to a preferred embodiment is shown. Docking station **300** preferably includes two stations, **306A** and **306B**, for receiving reaction blocks **140** of Type "A" and Type "B", respectively, as discussed above. As is known to those skilled in the art, docking station 300 may also be fitted with the proper motor,

gears, and other elements (not shown) necessary for docking station **300** to act as a vortexing shaker, and preferably as a vortexing shaker having a fixed displacement and variable speed.

Docking station **300** also preferably includes three locking linkages **304** for locking onto pins **180** on reaction blocks **140**. Each station **306** includes gas outlet connectors **308A** through **308D** which connect to ports **196A** through **196D**, respectively in reaction block **140** (see **Figure 9**). Each station **306** also includes two coolant or heating fluid (i.e., gas or liquid) connectors **310A** and **310B**. **Figure 1** shown fluid lines **320A** and **320B** attached to connectors **310A** and **310B**, respectively. Although not shown in **Figures 1** and **13**, independently controllable fluid lines attach to each connector shown in docking station **300**. Connectors **310A** and **310B** connect to ports **202A** and **202B**, respectively in reaction block **140** (See **Figure 9**). A gas outlet connector **312** which connects to gas inlet port **200** of reaction block **140** is also included in each station **306**.

Finally, stations **306A** and **306B** each include a magnetic reed switch **314A** and **314B**, respectively, which senses the presence of magnet **204** on reaction block **140**. Station **306A**, and more specifically the placement of port **312**, is arranged such that only an A-type reaction block **140** can be fully inserted and locked into position. Similarly, station **306B**, and more specifically the placement of port **312**, is arranged such that only a B-type reaction block **140** can be fully inserted and locked into position.

Referring now to **Figure 14**, a cross sectional view of a connector **308A** inserted into port **196A** of reaction block **140** is shown. Although only the interface between connector **308A** and **196A** will be discussed, it will be understood that similar interfaces are preferably included in other connections between reaction block **140**

and docking station **300**. In a preferred embodiment, connector **308A** is inserted into port **196A**. In this fashion, connector **308A** acts as a guide pin to ensure proper alignment of reaction block **140** with station **306A**. A gas-tight seal between connector **308A** and port **196A** is preferably provided by quad ring **330**. A quad ring is preferred over a standard o-ring because a quad ring has less tendency to adhere to surfaces when connector **308A** is removed from port **196A**.

Referring now to **Figures 15 and 16** an alternative embodiment of port **196A** is shown. In operations where inert or other atmosphere must be maintained, a normally closed valve, such as schraeder valve **360** may be placed in port **196A**. Schraeder valve **360** may be replaced with a bi-directional elastomeric valve. In operation, connector **308A** is inserted into port **196A** and engages pin **362** of schraeder valve **360**. Connector **308A** also forms a seal against quad ring **330**. Gas flows out of opening **364** and through schraeder valve **360**.

When connector **308A** is removed from port **196A**, pin **362** of schraeder valve **360** moves downward, creating a gas-tight seal. Again, this allows reaction block **140** to be moved from place to place while maintaining a desired atmosphere.

Pipetting work station **250** (see **Figure 1**) is preferably constructed such that operation of the work station cannot take place unless magnetic reed switches **314A** and **314B** detect the presence of one or both reaction blocks **140**. That is, pipetting work station **250** will not operate unless reaction blocks **140** are properly mounted in stations **306A** and **306B**.

LOCKING REAGENT CONTAINER RACK

As was discussed above, pipetting reagents under inert atmosphere is often essential during the synthesis of combinatorial libraries. However, when pipetting reagents from a relatively lightweight septum-sealed

container, the friction between the pipetting needle and the septum may be enough to lift the container from its resting position. This is obviously not desirable, as movement of and damage to the container and other equipment may result. Referring now to **Figures 1, 11, and 12**, a preferred embodiment of a locking reagent container rack **90** for pipetting under inert atmosphere is shown. Rack **90** includes a bottom plate or grating **92**, preferably coated with a layer of rubber or soft material **94**. Rack **90** may include one or more horizontal support plates **96**, and includes a plurality of vertical support members **98**. Horizontal plates **96** preferably include 48 circular openings **97** into which the containers **44** can be inserted. Rack **90** is preferably arranged such that septum-sealed containers **44** can be arranged in a 4 x 8 array.

A top plate **100** rests on top of vertical support members **98** and snugly against containers **44**. Top plate **100** preferably includes 48 circular openings **102** into which the tops of containers **44** can be inserted. Each opening **102** is preferably encircled with a rubber ring **104** to protect containers **44**.

Plate **100** also includes one or more fasteners (such as quarter turn wing-nut type fasteners) **105** which fasten plate **100** to vertical support members **98**, thus keeping containers **44** in place. Locking rack **90** may itself be fastened to a work surface (such as work station deck **254**), although the weight of rack **90** and containers **44** would probably be sufficient to prevent any motion caused by friction between a pipetting needle and a septum.

EXAMPLE OF OPERATION

The many features of the preferred embodiments described above facilitate the relatively quick and efficient generation of chemical libraries. In the following discussion, a synthesis operation involving a

type "A" reaction block **140** will be discussed. However, it will be understood that the following discussion will apply equally for a type "B" block as well.

In a typical operation, a synthesis support such as solid phase resin is deposited onto each frit **124** in reaction chambers **110**. Reaction block **140** is then assembled as shown in **Figure 4**. Bottom seal **220** may be mounted if reaction block **140** must be moved from place to place while maintaining a desired atmosphere or pressure.

Reaction block **140** may then be manually or robotically inserted into station **306A** of docking station **300** on work station **250** (see **Figures 1** and **13**). At this point, microtiter plate **302** is not located in station **306A**. Locking linkages **304** then grip pins **180**, locking reaction block **140** into place. A type "B" reaction block may be simultaneously mounted in station **306B**.

Pipetting work station **250** then operates under computer control to deliver the chosen combination of reagents into reaction chambers **110**. Specifically, pipetting needle **22** (as controlled by pipetting arm **252**) is used to transfer reagents from septum **46** sealed containers **44** into septum **253** sealed reaction chambers **110**. The interior and exterior of pipetting needle **22** may be cleaned as necessary in rinse stations **70**. At any time that reaction block **140** is mounted in station **306A**, reaction block **140** may be heated or cooled, pressurized with inert gas, or vortexed as described above.

For reactions that take a considerable amount of time, reaction block **140** may be manually or robotically moved to another docking station **300**, or to some other location while the reactions are taking place. After the synthesis of the desired products has been completed, the products may be cleaved from the synthesis supports using

the appropriate reagents. These reagents may be applied at work station **250**, or they may be applied robotically at some other location. If bottom seal **220** had been mounted, it is then removed, and reaction block **140** is mounted onto a microtiter plate **302** in station **306A**. Reaction chambers **110** are then pressurized, forcing the product out drain tubes **138** and into alternate wells of microtiter plate **302**. Microtiter plate **302** is then moved to station **306B**. A type "B" reaction block **140** is mounted on microtiter plate **302**, and product is then deposited into the alternate empty wells of microtiter plate **302** as discussed above. Again, this process allows product to be deposited directly into the wells of a standard microtiter plate, without requiring an intermediate step.

The present invention has been described in terms of a preferred embodiment. The invention, however, is not limited to the embodiment depicted and described. Rather, the scope of the invention is defined by the appended claims.

WHAT IS CLAIMED IS:

1. A reaction chamber comprising:

a generally cylindrical upper body having a top opening, an inner surface, an outer surface, and an inside diameter;

a generally cylindrical lower body coaxial with the upper body;

the lower body having an inner surface, an outer surface, and an inside diameter smaller than the inside diameter of the upper body;

a tapered section connecting the upper body to the lower body; and

a drain tube having an inside surface and connected to the lower body.

2. A reaction chamber as in claim 1 wherein the drain tube is connected to the lower body with a funnel-shaped section.

3. A reaction chamber as in claim 1 wherein the top opening of the upper body has a rounded edge to facilitate sealing against a septum.

4. A reaction chamber as in claim 1 wherein the upper body includes a port connecting the inner surface of the upper body to the outer surface of the upper body.

5. A reaction chamber as in claim 4 wherein the port is a gas inlet port.

6. A reaction chamber as in claim 1 wherein the drain tube is connected to an s-shaped trap tube having an inlet opening and an outlet opening.

7. A reaction chamber as in claim 6 wherein the drain tube has an annular bead on its inside surface to facilitate sealing with the inlet opening of the s-shaped trap tube.

8. A reaction chamber as in claim 7 wherein the s-shaped trap tube is welded to the drain tube.

9. A reaction chamber as in claim 6 wherein the s-shaped trap tube extends upwardly along the length of the upper body.

10. A reaction chamber as in claim 9 wherein the outlet port of the s-shaped trap tube points downward.

11. A reaction chamber as in claim 10 wherein the outlet port of the s-shaped trap tube is connected to a second cylindrical drain tube.

12. A reaction chamber as in claim 11 wherein the second cylindrical drain tube is of a larger diameter than the trap tube.

13. A reaction chamber as in claim 12 wherein the s-shaped trap tube and the second cylindrical drain tube are made from extruded polypropylene or teflon.

14. A reaction chamber as in claim 1 wherein the upper body, the lower body, the tapered section, the funnel shaped section, and the drain tube are made from a single piece of injection-molded polymer.

15. A reaction chamber as in claim 14 wherein the polymer is polypropylene or teflon.

16. A reaction chamber as in claim 1 wherein the upper body has a volume of approximately 2 ml.

17. A reaction chamber as in claim 1 wherein the upper body further includes a keying protrusion on its outer surface.

18. A reaction chamber as in claim 1 wherein the lower body further includes a frit having a diameter smaller than the inside diameter of the lower body portion.

19. A reaction chamber as in claim 18 wherein the frit is press fit into the lower body portion.

20. A reaction chamber as in claim 19 wherein the frit is made of polyethylene.

21. A reaction chamber comprising:

a generally cylindrical upper body having a top opening, an inner surface, an outer surface, and an inside diameter;

a generally cylindrical lower body coaxial with the upper body;

the lower body having an inner surface, an outer surface, and an inside diameter smaller than the inside diameter of the upper body;

means for connecting the upper body to the lower body;

a drain tube having an inside surface; and means for connecting the drain tube to the lower body.

22. A reaction chamber as in claim 21 wherein the means for connecting the drain tube to the lower

body is a funnel-shaped section.

23. A reaction chamber as in claim 21 wherein the means for ~~connecting the upper body to the lower~~ body is a tapered section.

24. A reaction chamber as in claim 21 wherein the top opening of the upper body has a rounded edge to facilitate sealing against a septum.

~~25.~~ A reaction chamber as in claim 21 wherein the upper body includes a means for connecting the inner surface of the upper body to the outer surface of the upper body.

26. A reaction chamber as in claim 25 wherein the means for connecting the inner surface of the upper body to the outer surface of the upper body port is a gas inlet port.

27. A reaction chamber as in claim 21 wherein the drain tube is connected to an s-shaped trap tube having an inlet opening and an outlet opening.

28. A reaction chamber as in claim 27 wherein the drain tube has an annular bead on its inside surface to facilitate sealing with the inlet opening of the s-shaped trap tube.

29. A reaction chamber as in claim 28 wherein the s-shaped trap tube is welded to the drain tube.

30. A reaction chamber as in claim 27 wherein the s-shaped trap tube extends upwardly along the length of the upper body.

31. A reaction chamber as in claim 30 wherein the outlet port of the s-shaped trap tube points downward.

32. A reaction chamber as in claim 31 wherein the outlet port of the s-shaped trap tube is connected to a second cylindrical drain tube.

33. A reaction chamber as in claim 32 wherein the second cylindrical drain tube is of a larger diameter than the trap tube.

34. A reaction chamber as in claim 33 wherein the s-shaped trap tube and the second cylindrical drain tube are made from extruded polypropylene or teflon.

35. A reaction chamber as in claim 21 wherein the upper body, the lower body, the tapered section, the funnel shaped section, and the drain tube are made from a single piece of injection-molded polymer.

36. A reaction chamber as in claim 35 wherein the polymer is polypropylene or teflon.

37. A reaction chamber as in claim 21 wherein the upper body has a volume of approximately 2 ml.

38. A reaction chamber as in claim 21 wherein the upper body further includes a keying protrusion on its outer surface.

39. A reaction chamber as in claim 21 wherein the lower body further includes means for retaining a frit.

40. A reaction chamber as in claim 39 wherein the frit is press fit into the lower body portion.

41. A reaction chamber as in claim 40 wherein the frit is made of polyethylene.

42. A reaction chamber comprising:

a generally cylindrical upper body having a top opening with a rounded edge to facilitate sealing against a septum, an inner surface, an outer surface, a gas port connecting the inner surface with the outer surface, and an inside diameter;

a generally cylindrical lower body coaxial with the upper body;

the lower body having an inner surface with an annular bead for retaining a frit, an outer surface, and an inside diameter smaller than the inside diameter of the upper body;

a tapered section connecting the upper body to the lower body;

a drain tube having an inside surface;

and a funnel shaped section connecting the drain tube to the lower body.

43. A reaction block comprising:

a first side wall and a second side wall, the first and second side walls having a first width and a first height;

a first end wall and a second end wall, the first and second end walls having a second width narrower than the first width, and the first height;

a top surface bordered by the first and second side walls and the first and second end walls, the top surface having:

a plurality of generally circular openings for removably receiving a plurality of

reaction chambers, the reaction chambers each having a circular opening and a top surface;

a gas port;

and a plurality of raised beads defining the edges of a plurality of chambers;

the raised beads having a top surface which is in approximately the same plane as the top surface of the reaction chambers;

a flexible septum which seals against the top surfaces of the reaction chambers and the raised beads;

and a retainer plate which covers the septum.

44. A reaction block as in claim 43 wherein the retainer plate has a plurality of openings which spatially correspond to the openings of the reaction chambers.

45. A reaction block as in claim 44 wherein the retainer plate is held securely against the septum and the reaction block with a plurality of fasteners.

46. A reaction block as in claim 43 wherein the top surface includes a first, a second, a third, and a fourth, separately controllable gas inlet ports, and wherein the raised beads define a first, a second, a third, and a fourth pressurization chambers.

47. A reaction block as in claim 46 wherein each pressurization chamber includes an equal number of the reaction chambers.

48. A reaction block as in claim 46 wherein each pressurization chamber includes 12 reaction chambers.

49. A reaction block as in claim 46 wherein the first, second, third, and fourth separately controllable gas inlet ports are in communication with the first, second, third, and fourth pressurization chambers, respectively.

50. A reaction block as in claim 47 wherein each of the pressurization chambers includes a waste basin which is recessed below the level of the top surfaces of the reaction chambers.

51. A reaction block as in claim 50 wherein each of the four pressurization chambers has 12 of the reaction chambers.

52. A reaction block as in claim 43 wherein each of the generally circular openings on the top surface have a keying notch, and wherein each of the reaction chambers have a keying protrusion.

53. A reaction block as in claim 43 wherein the block is made of aluminum.

54. A reaction block as in claim 53 wherein the block is made of 6061 aluminum.

55. A reaction block as in claim 53 wherein the aluminum has been anodized.

56. A reaction block as in claim 43 wherein the block is color coded.

57. A reaction block as in claim 43 wherein the block has an identification number.

58. A reaction block as in claim 43 wherein the septum is made from thermoplastic rubber.

59. A reaction block as in claim 58 wherein the septum is die cut with six registration holes and four access holes.

60. A reaction block as in claim 43 wherein the first and second side walls are fitted with one pin each to facilitate securing the block to a work station.

61. A reaction block as in claim 43 wherein the first and second end walls are fitted with two pins each to facilitate handling by a robotic gripper.

62. A reaction block as in claim 43 further including a bottom surface defined by the bottom edges of the first and second side walls and the first and second end walls, the bottom surface being parallel to the top surface.

63. A reaction block as in claim 43 further including a first, second, third and fourth gas inlet ports in communication with the first, second, third, and fourth gas outlet ports of the top surface, respectively.

64. A reaction block as in claim 63 wherein the first, second, third and fourth gas inlet ports are in the bottom surface.

65. A reaction block as in claim 43 further including an input port for receiving heating or cooling fluid.

66. A reaction block as in claim 65 wherein the input port for receiving heating or cooling fluid is in the bottom surface.

67. A reaction block as in claim 65 further including an output port for draining heating or cooling fluid.

68. A reaction block as in claim 67 wherein the output port for draining heating or cooling fluid is on the bottom surface.

69. A reaction block as in claim 68 further including a plurality of passages connecting the input port for receiving heating or cooling fluid to the output port for draining heating or cooling fluid.

70. A reaction block as in claim 62 wherein the bottom surface includes a magnet.

71. A reaction block as in claim 70 wherein the magnet is a bar magnet.

72. A reaction block as in claim 62 wherein each of the reaction chambers includes a drain tube.

73. A reaction block as in claim 72 further including a cavity extending upwardly from the bottom surface to a middle surface, the middle surface parallel to the top surface and the bottom surface.

74. A reaction block as in claim 73 wherein the middle surface has openings for receiving the drain tubes.

75. A reaction block as in claim 74 wherein the cavity includes a machined step to facilitate mating with a microtiter plate.

76. A reaction block as in claim 75 wherein the cavity includes a second machined step to facilitate mating with a bottom seal.

77. A reaction block as in claim 76 wherein the bottom seal includes an o-ring which seals against the second machined step.

78. A reaction block as in claim 76 wherein the bottom seal includes a one-way pressure valve.

79. A reaction block as in claim 63 wherein the first, second, third and fourth gas inlet ports include a valve.

80. A reaction block as in claim 80 wherein the valve is a schraeder valve.

81. A reaction block as in claim 80 wherein the valve is a bi-directional elastomeric valve.

82. A reaction block comprising:

a first side wall and a second side wall, the first and second side walls having a first width and a first height;

a first end wall and a second end wall, the first and second end walls having a second width narrower than the first width, and the first height;

a top surface bordered by the first and second side walls and the first and second end

walls, the top surface having:

a plurality of generally circular openings for removably receiving a plurality of reaction chambers, the reaction chambers each having a circular opening and a top surface;

a gas port; and

a plurality of raised beads defining the edges of a plurality of chambers;

the raised beads having a top surface which is in approximately the same plane as the top surface of the reaction chambers;

means for sealing against the top surfaces of the reaction chambers and the raised beads;

and a retainer plate which covers the means for sealing.

83. A reaction block as in claim 83 wherein the retainer plate has a plurality of openings which spatially correspond to the openings of the reaction chambers.

84. A reaction block as in claim 84 further including means for fastening the retainer plate to the means for sealing the reaction block.

85. A reaction block as in claim 83 wherein the top surface includes a first, a second, a third, and a fourth, separately controllable gas inlet ports, and wherein the raised beads define a first, a second, a third, and a fourth pressurization chambers.

86. A reaction block as in claim 86 wherein each of the four pressurization chambers includes an equal number of the reaction chambers.

87. A reaction block as in claim 87 wherein the first, second, third, and fourth separately controllable gas inlet ports are in communication with the first, second, third, and fourth pressurization chambers, respectively.

88. A reaction block as in claim 87 wherein each of the four pressurization chambers includes a waste basin which is recessed below the level of the top surfaces of the reaction chambers.

89. A reaction block as in claim 87 wherein each of the four chambers has 12 of the reaction chambers.

90. A reaction block as in claim 83 wherein each of the generally circular openings on the top surface have a keying notch, and wherein each of the reaction chambers have a keying protrusion.

91. A reaction block as in claim 83 wherein the block is made of aluminum.

92. A reaction block as in claim 92 wherein the block is made of 6061 aluminum.

93. A reaction block as in claim 92 wherein the aluminum has been anodized.

94. A reaction block as in claim 83 wherein the block is color coded.

95. A reaction block as in claim 83 wherein the block has an identification number.

96. A reaction block as in claim 83 wherein the block has a bar code.

97. A reaction block as in claim 83 wherein the means for sealing is a septum

98. A reaction block as in claim 98 wherein the septum is made from thermoplastic rubber.

99. A reaction block as in claim 99 wherein the septum is die cut with six registration holes and four access holes.

100. A reaction block as in claim 83 wherein the first and second side walls are fitted with one pin each to facilitate securing the block to a work station.

101. A reaction block as in claim 83 wherein the first and second end walls are fitted with two pins each to facilitate handling by a robotic gripper.

102. A reaction block as in claim 83 further including a bottom surface defined by the bottom edges of the first and second side walls and the first and second end walls, the bottom surface being parallel to the top surface.

103. A reaction block as in claim 83 further including a first, second, third and fourth gas inlet ports in communication with the first, second, third, and fourth gas outlet ports of the top surface, respectively.

104. A reaction block as in claim 104 wherein the first, second, third and fourth gas inlet ports are in the bottom surface.

105. A reaction block as in claim 83 further

including an input port for receiving heating or cooling fluid.

106. A reaction block as in claim 106 wherein the input port for receiving heating or cooling fluid is in the bottom surface.

107. A reaction block as in claim 106 further including an output port for draining heating or cooling fluid.

108. A reaction block as in claim 108 wherein the output port for draining heating or cooling fluid is on the bottom surface.

109. A reaction block as in claim 109 further including a plurality of passages connecting the input port for receiving heating or cooling fluid to the output port for draining heating or cooling fluid.

110. A reaction block as in claim 103 wherein the bottom surface includes a magnet.

111. A reaction block as in claim 111 wherein the magnet is a bar magnet.

112. A reaction block as in claim 103 wherein each of the reaction chambers includes a drain tube.

113. A reaction block as in claim 113 further including a cavity extending upwardly from the bottom surface to a middle surface, the middle surface parallel to the top surface and the bottom surface.

114. A reaction block as in claim 114 wherein the middle surface has openings for receiving the drain tubes.

115. A reaction block as in claim 115 wherein the cavity includes a machined step to facilitate mating with a microtiter plate.

116. A reaction block as in claim 116 wherein the cavity includes a second machined step to facilitate mating with a bottom seal.

117. A reaction block as in claim 117 wherein the bottom seal includes an o-ring which seals against the second machined step.

118. A reaction block as in claim 117 wherein the bottom seal includes a one-way pressure valve.

119. A reaction block as in claim 104 wherein the first, second, third and fourth gas inlet ports include a quad ring seal.

120. A reaction block as in claim 98 wherein the septum is made from an elastomeric material.

121. A reaction block as in claim 98 wherein the septum is made from an elastomeric material coated with teflon.

122. A container rack for use in a pipetting work station, comprising:

a bottom surface for supporting a plurality of septum sealed reagent containers;

a horizontal plate having a plurality of circular holes for receiving the containers;

a locking top plate having a plurality of circular holes aligned with the circular holes in the horizontal plate, and at least one fastener;

a plurality of vertical support members which support the locking top plate and the horizontal plate;

and a means for fastening the top plate to the vertical support members.

123. A rack as in claim 123 wherein the circular openings of the top plate are lined with a soft material.

124. A rack as in claim 124 wherein the soft material is rubber.

125. A docking station for receiving a reaction block having a plurality of gas inlet ports, comprising:

a platform including a cavity for removably receiving a reaction block;

a plurality of gas outlet connectors coupled to the gas inlet ports of the reaction block;

a reed switch which detects the presence of the reaction block; and

a linkage which locks the reaction block into the cavity.

126. A docking station as in claim 126 wherein the reaction block includes a bar magnet, and wherein the reed switch detects the presence of the bar magnet.

127. A docking station as in claim 126 further

including a heating or cooling fluid outlet connector coupled to a heating or cooling fluid inlet port on the reaction block.

128. A docking station as in claim 126 wherein the platform includes a first cavity of a first type for receiving a first reaction block of a first type, and a second cavity of a second type for receiving a second reaction block of a second type.

129. A docking station as in claim 127 wherein the gas outlet connectors fit into the gas inlet ports of the reaction blocks.

130. A docking station as in claim 128 wherein the gas outlet connectors are sealed against the gas inlet ports with quad rings.

131. A docking station as in claim 126 wherein said platform acts as a vortexing shaker.

132. A docking station for receiving a reaction block having a plurality of gas inlet ports, comprising:

a platform including means for removably receiving a reaction block;

means for connecting a supply of gas to the gas inlet ports of the reaction block;

means for detecting the presence of the reaction block;

and means for locking the reaction block into the means for removably receiving the reaction block.

133. A docking station as in claim 133 wherein the reaction block includes a bar magnet, and wherein the means for detecting detects the presence of the

bar magnet.

134. A docking station as in claim 133 further including means for connecting a source of heating or cooling fluid to a heating or cooling fluid inlet port on the reaction block.

135. A docking station as in claim 133 wherein the platform includes a first means for receiving a first reaction block of a first type, and a second means for receiving a second reaction block of a second type.

136. A docking station as in claim 133 wherein said platform acts as a vortexing shaker.

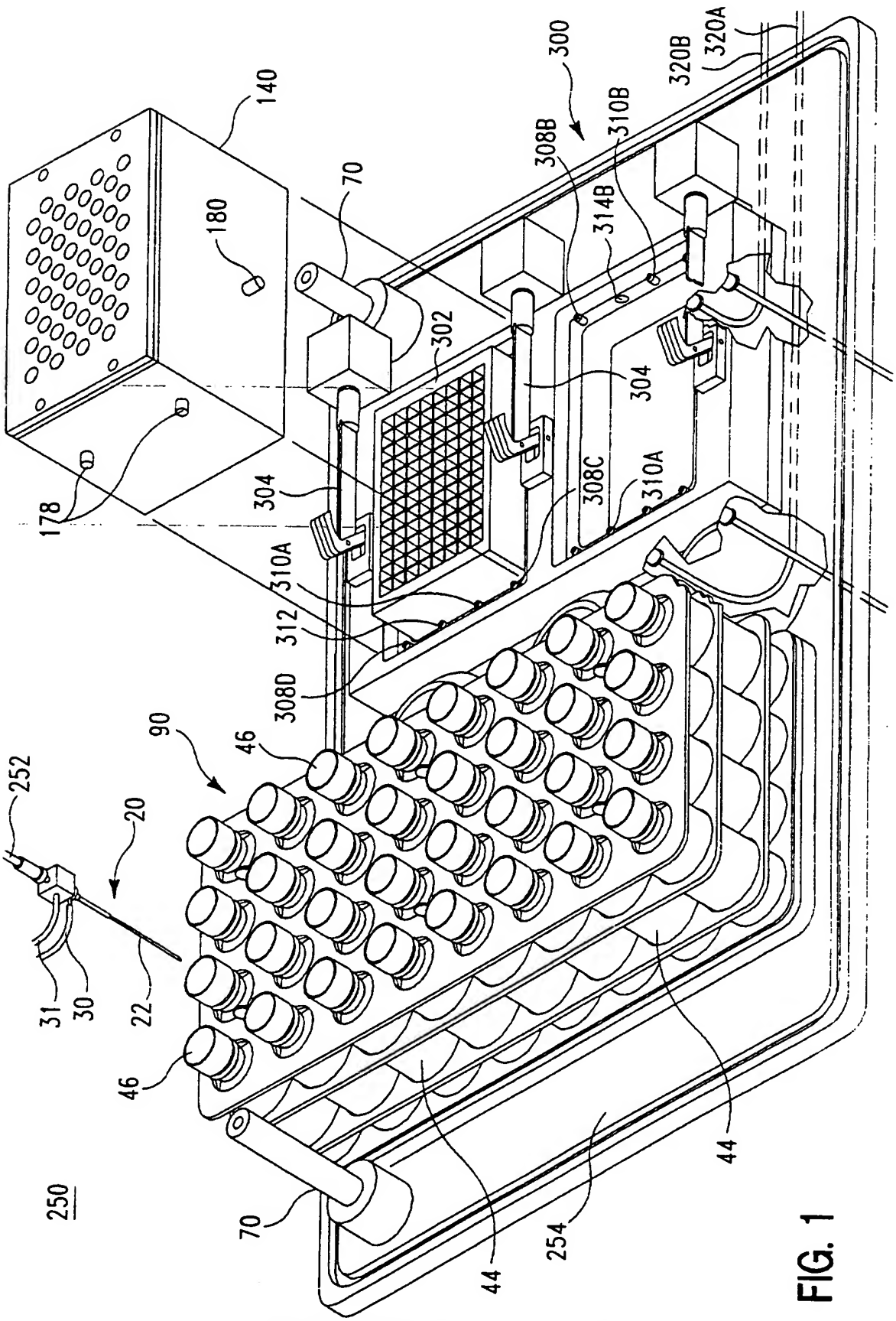
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FIG. 1

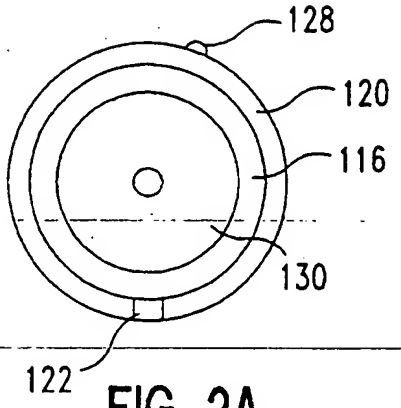


FIG. 2A

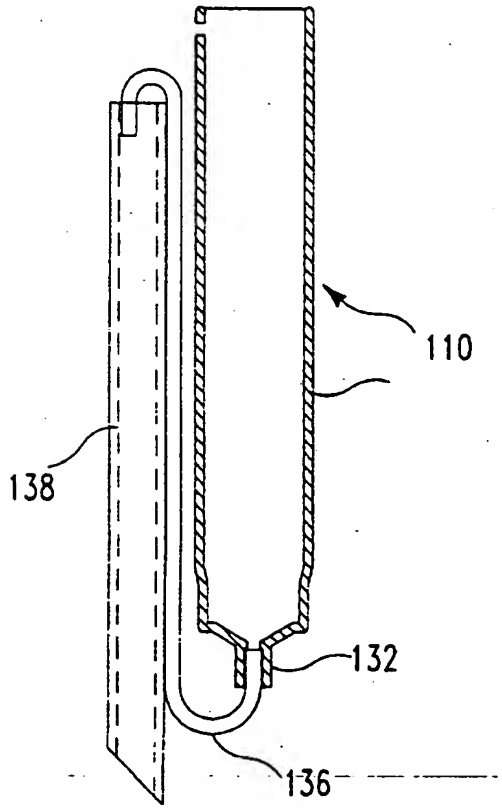


FIG. 3

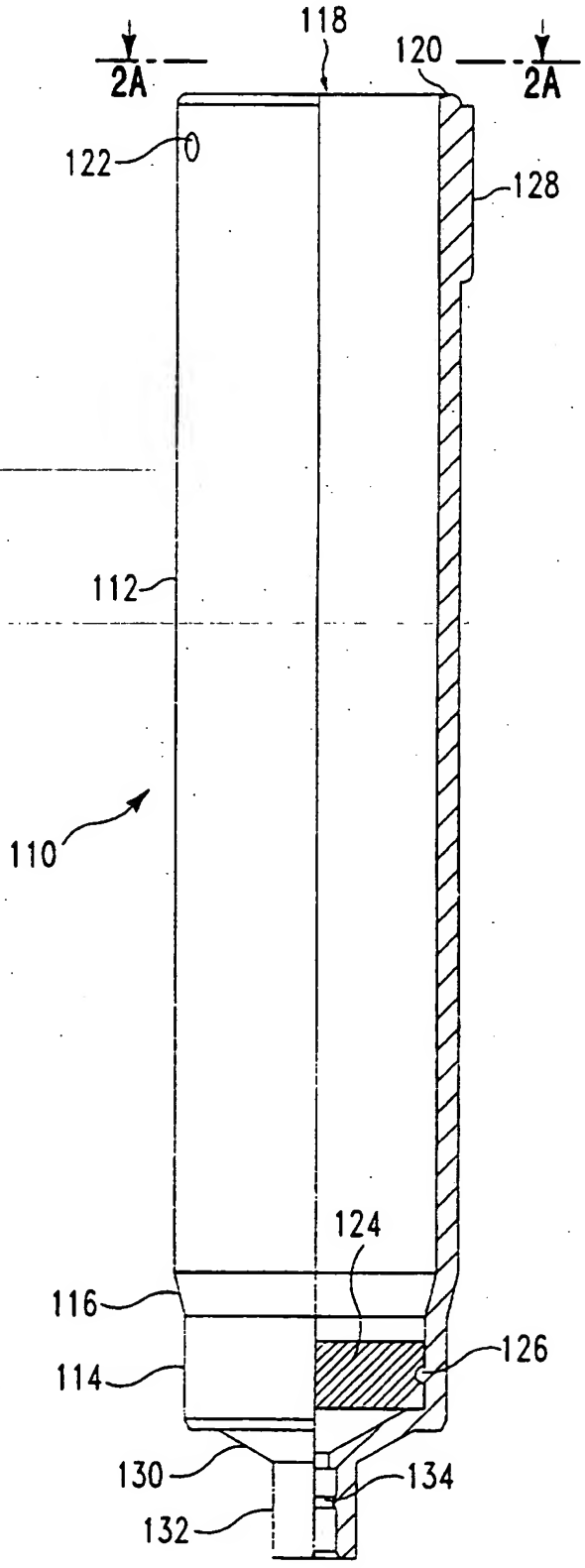
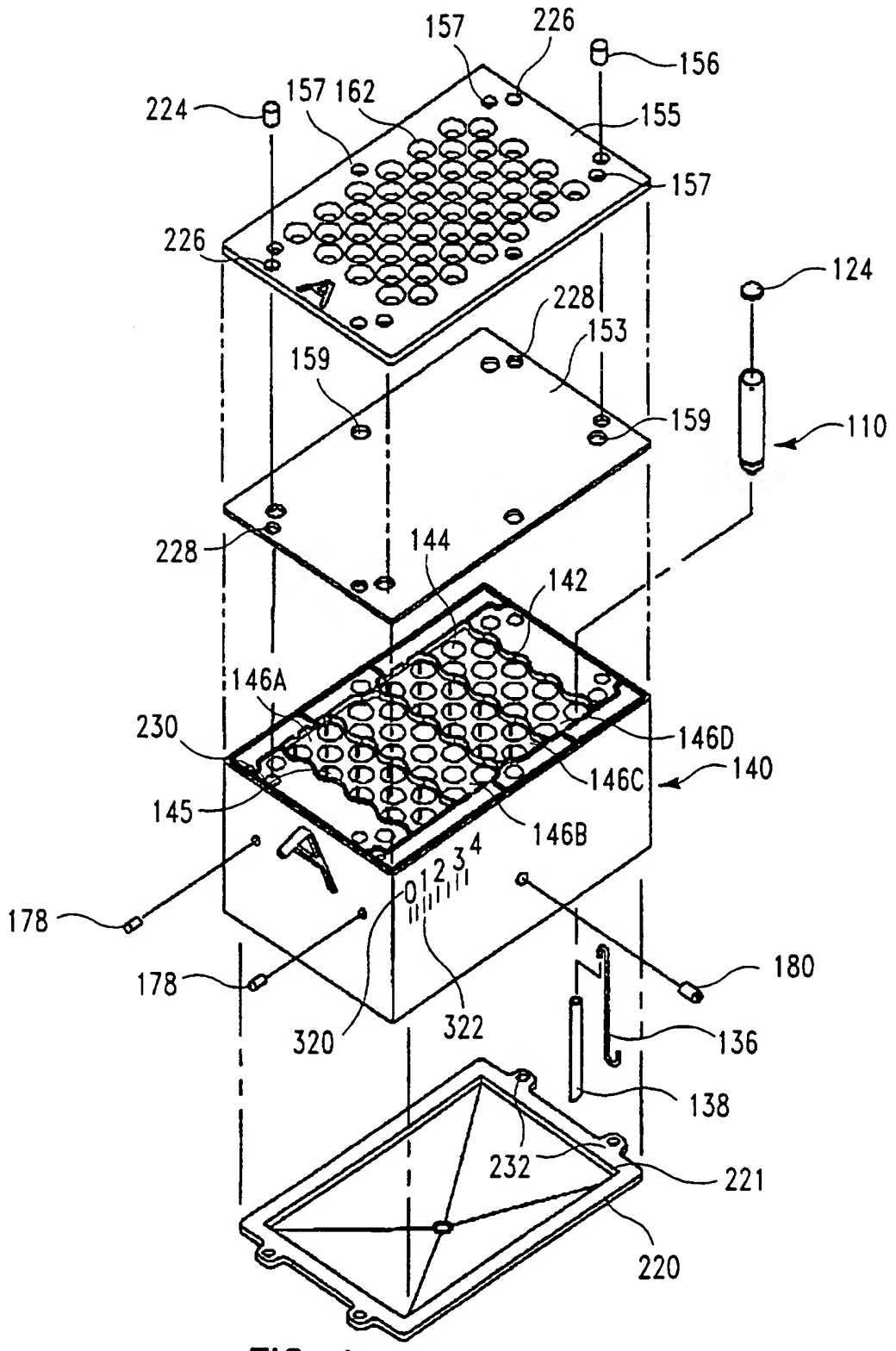


FIG. 2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146C
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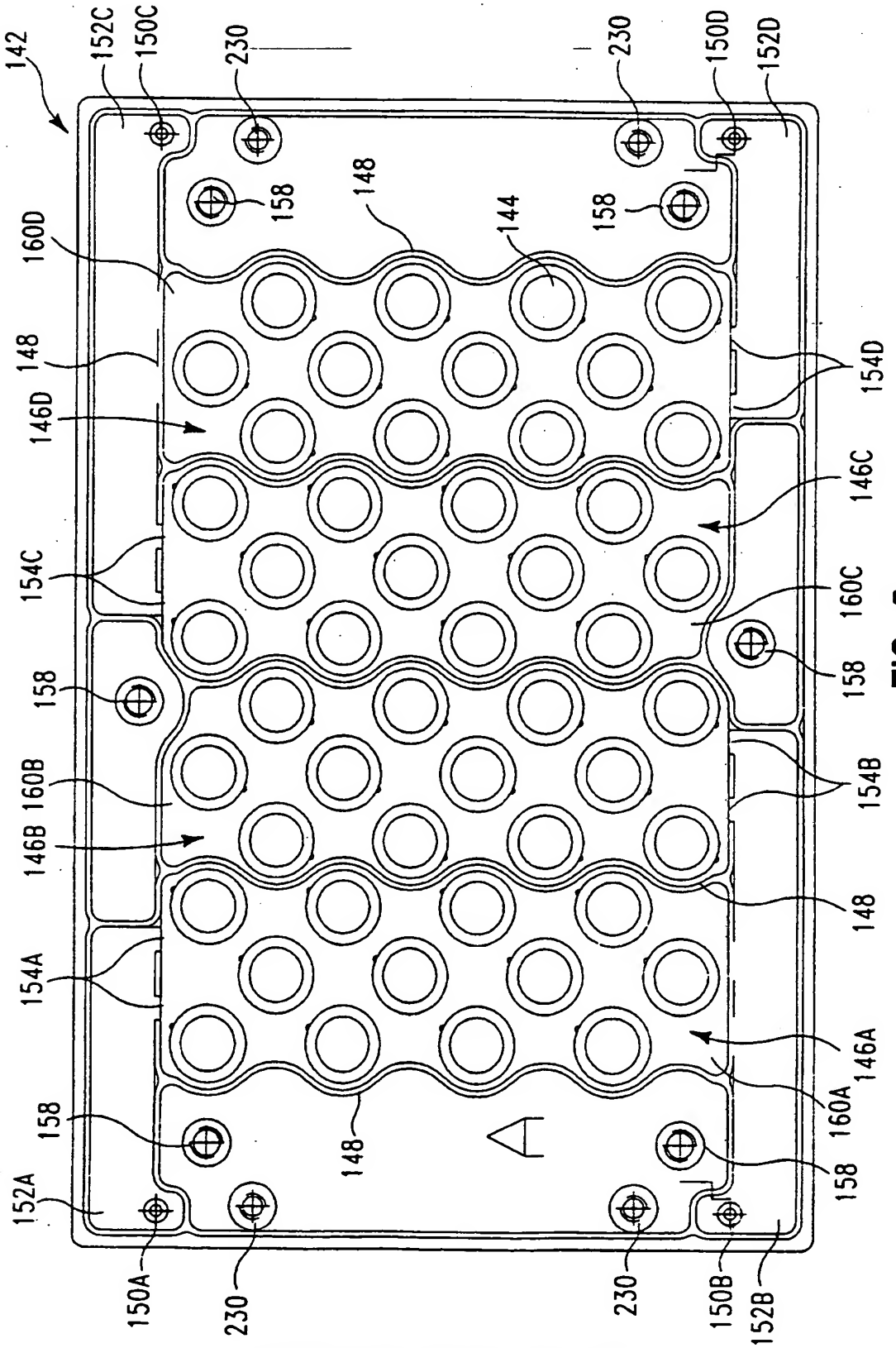
FIG. 4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152B

FIG. 5

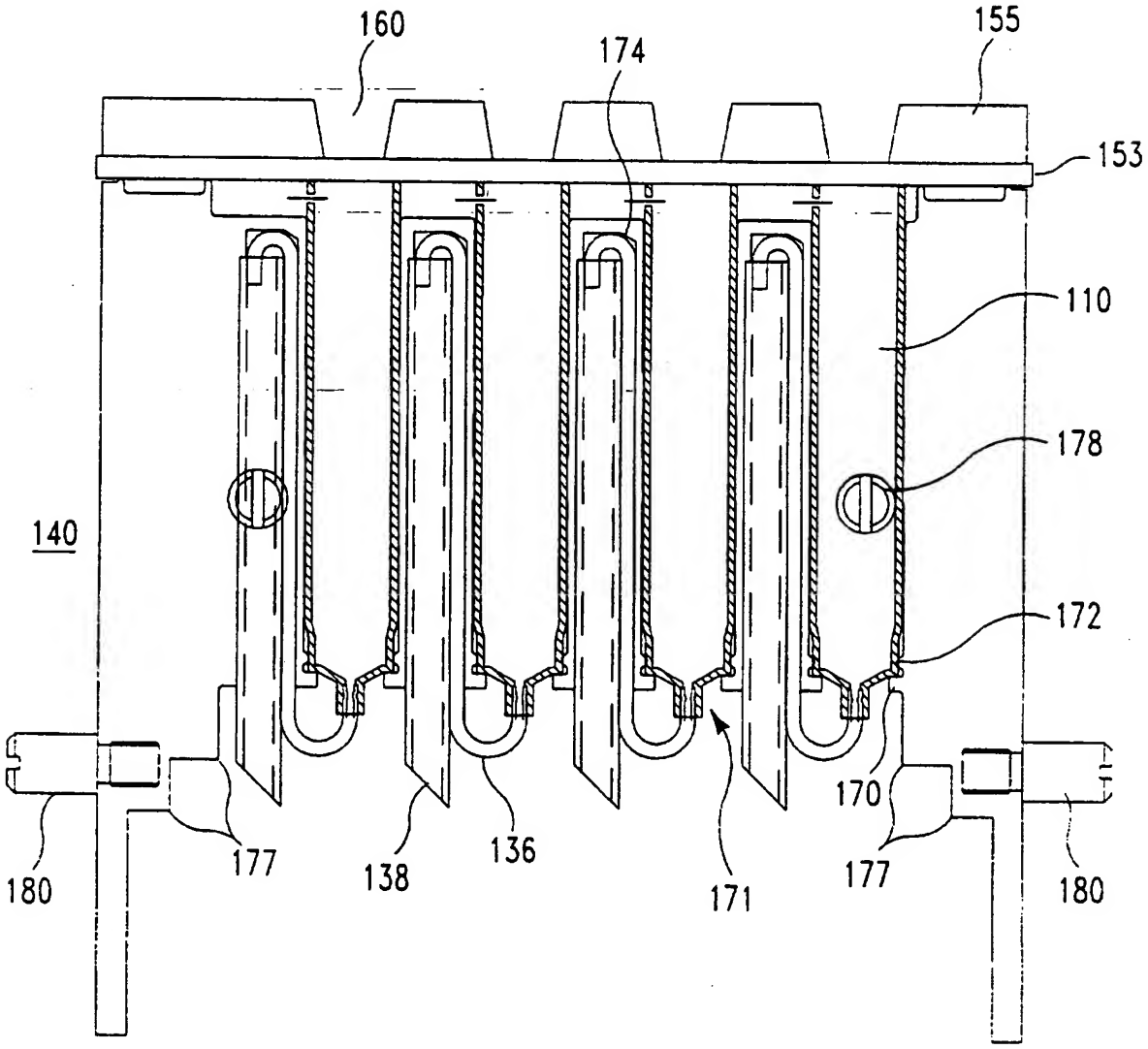


FIG. 6

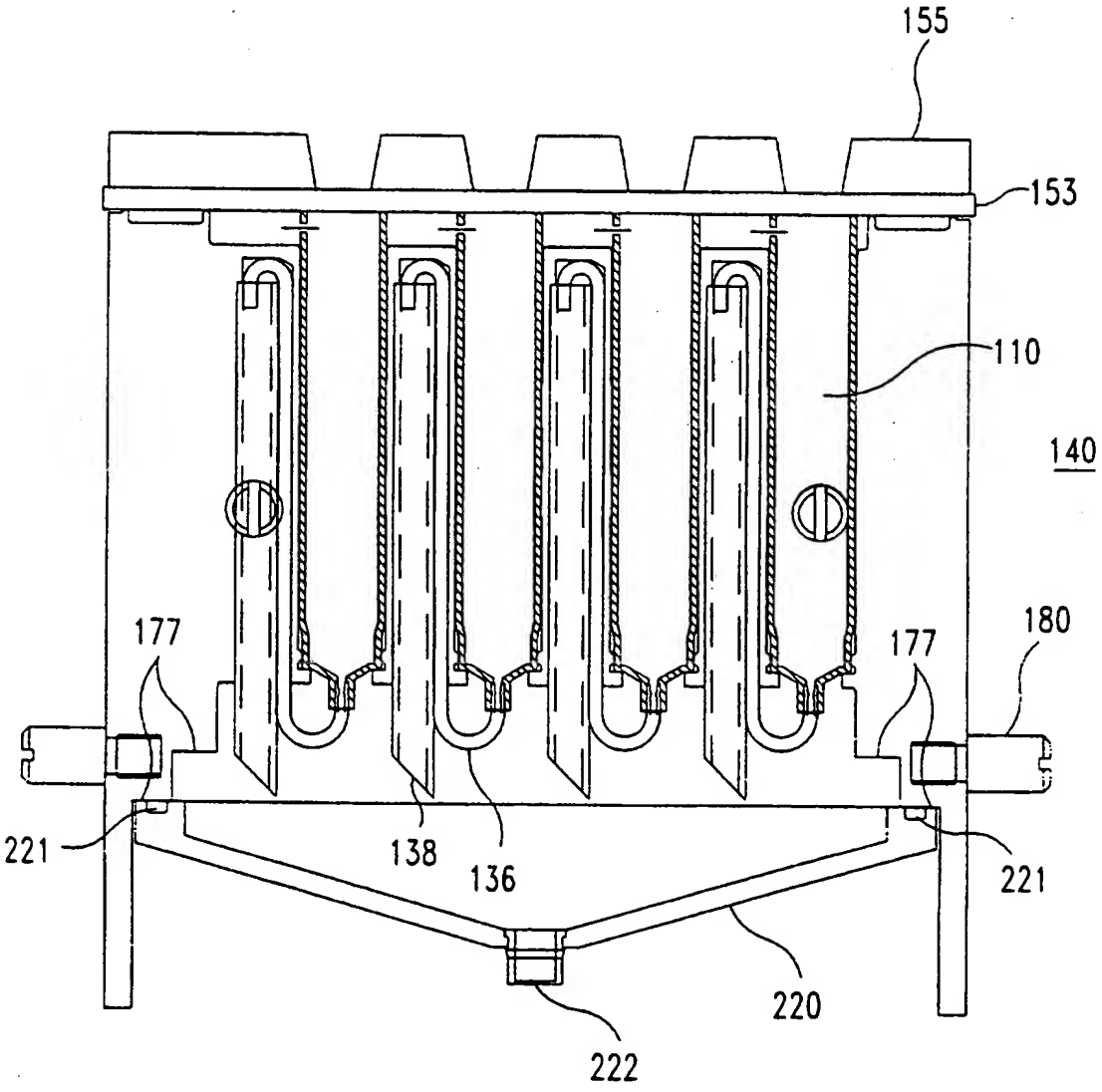


FIG. 7

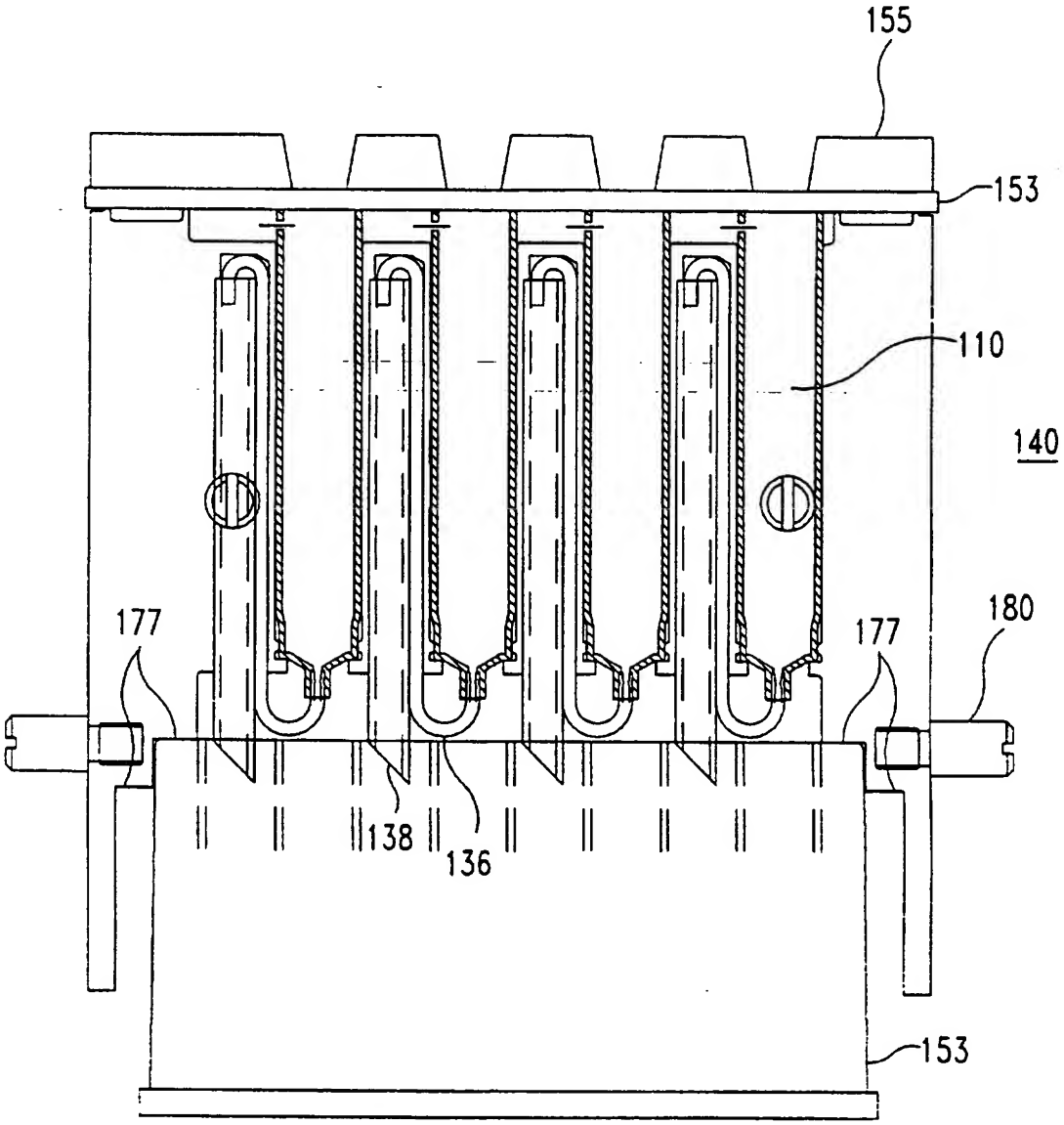
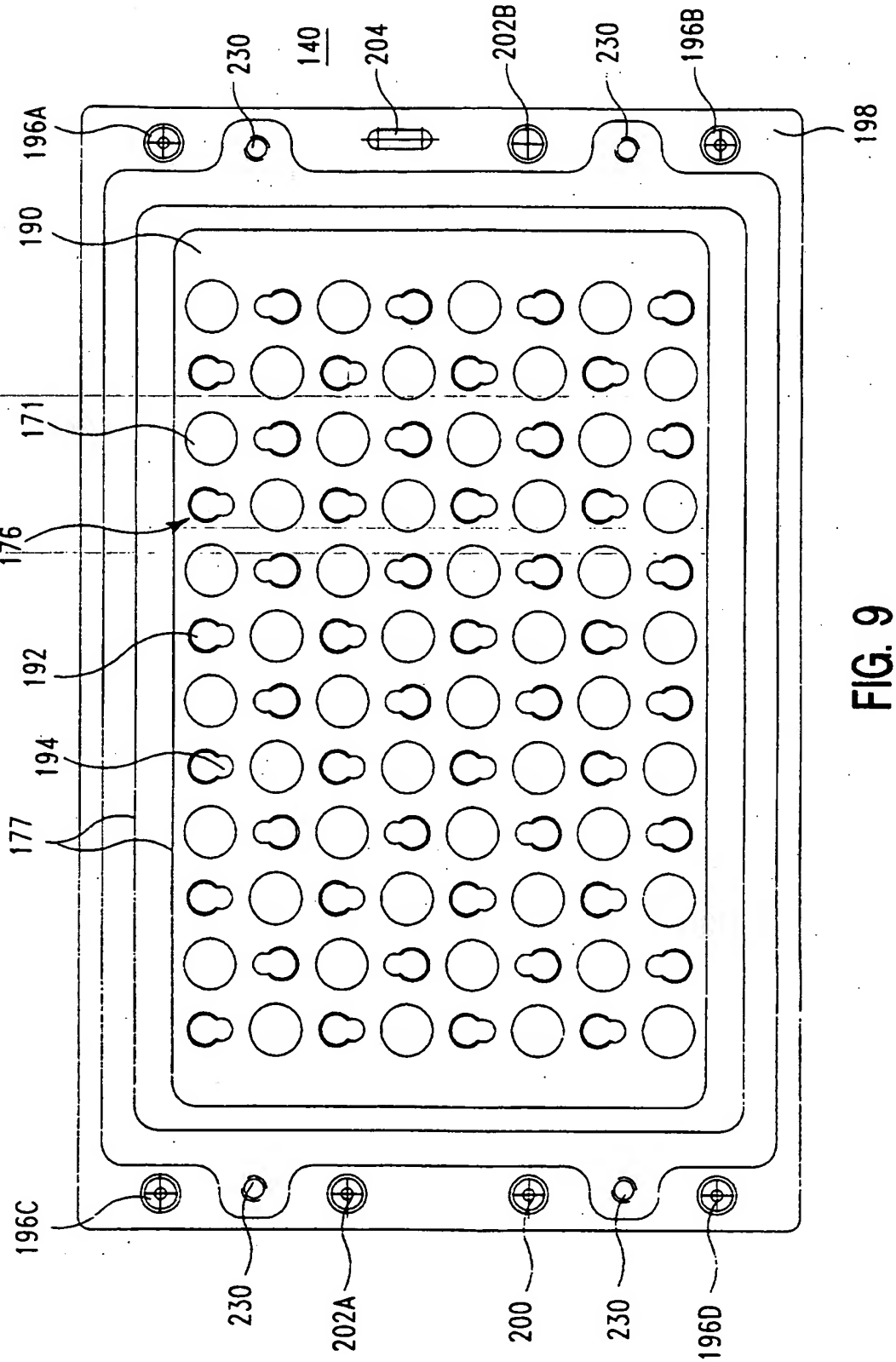


FIG. 8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196C
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202A
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230
196D

FIG. 9

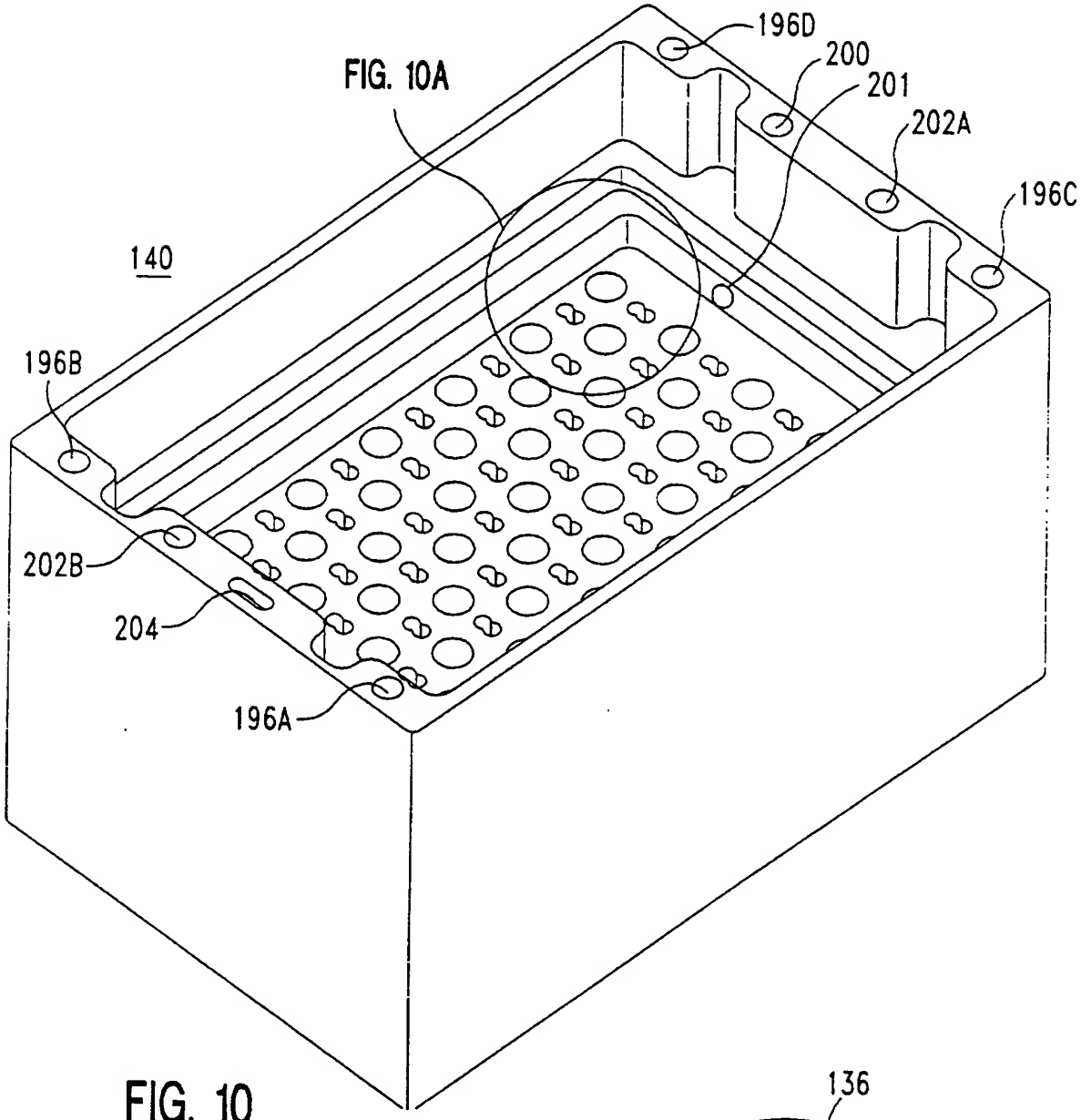


FIG. 10

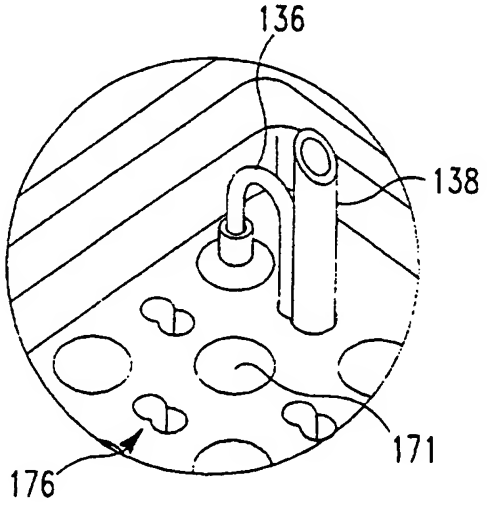


FIG. 10A

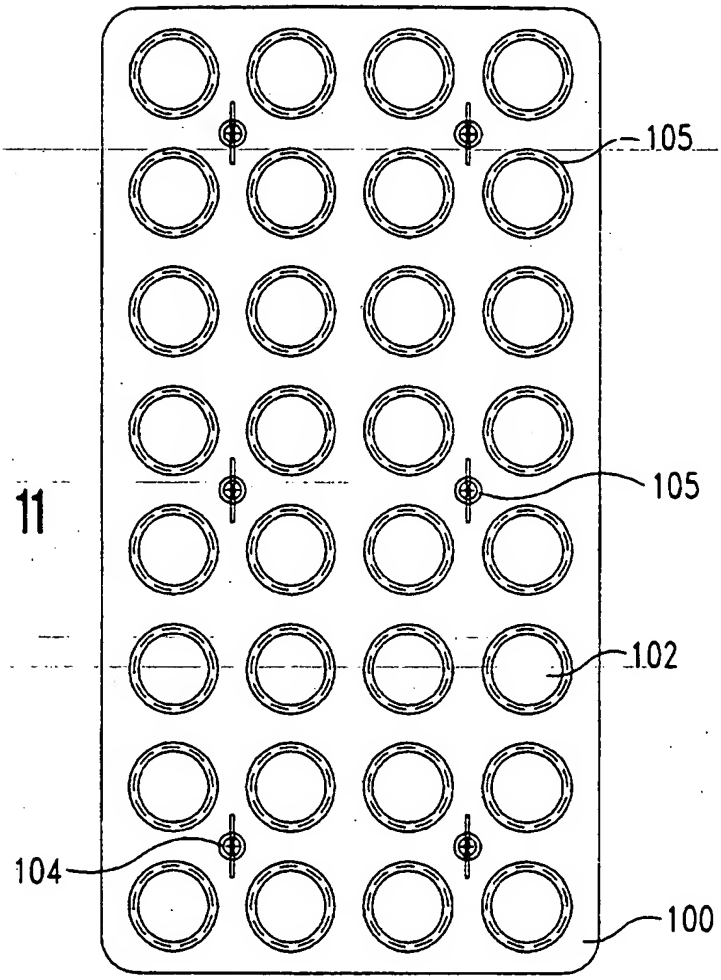


FIG. 11

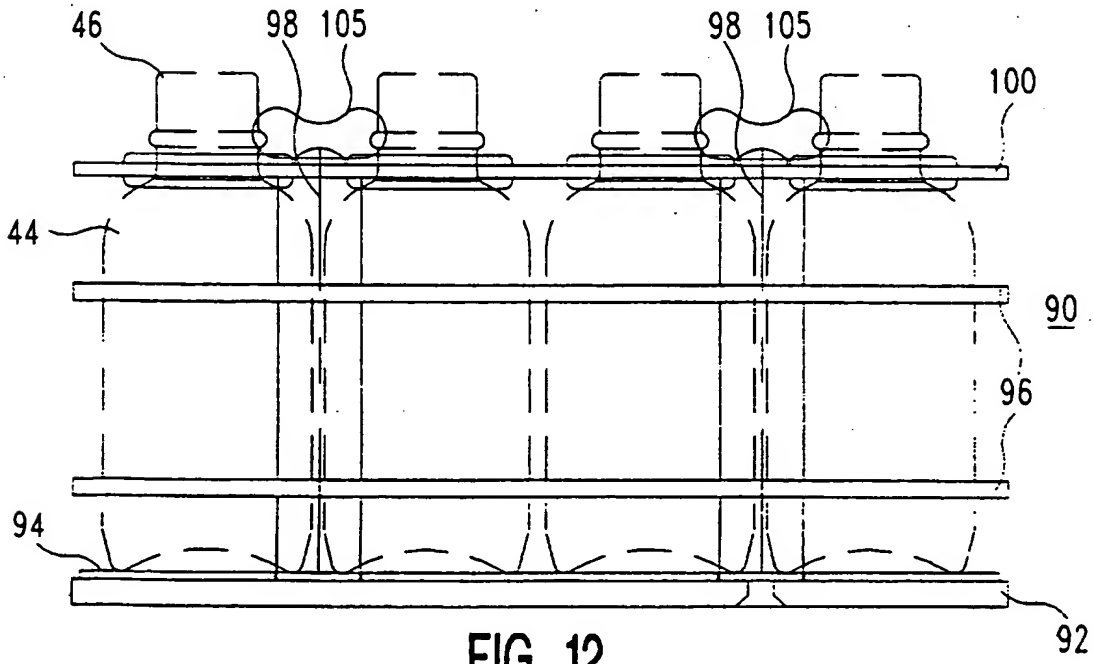
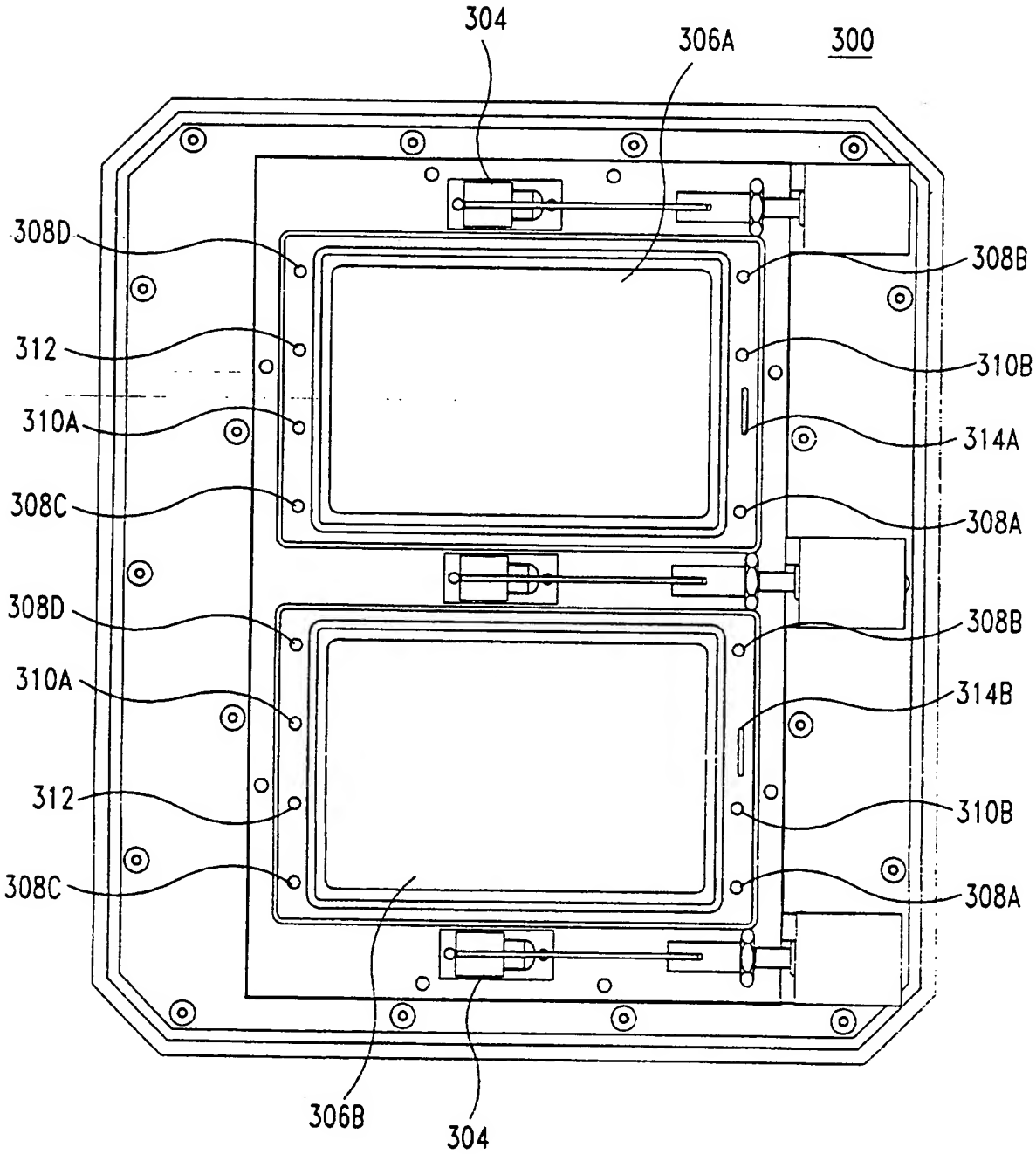


FIG. 12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310B
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306B
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FIG. 13

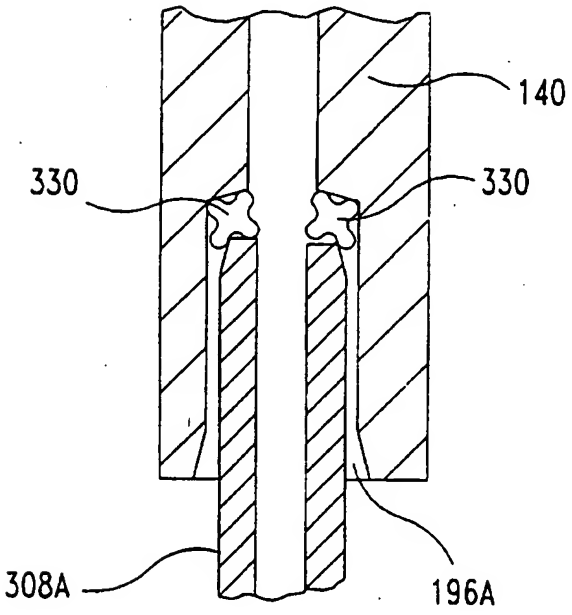

FIG. 14

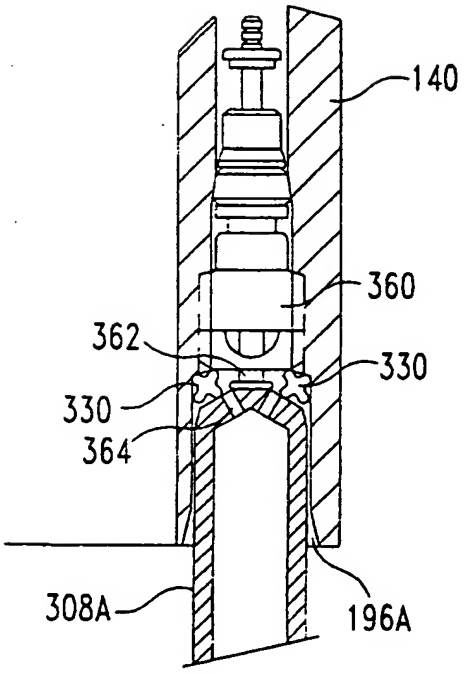

FIG. 15

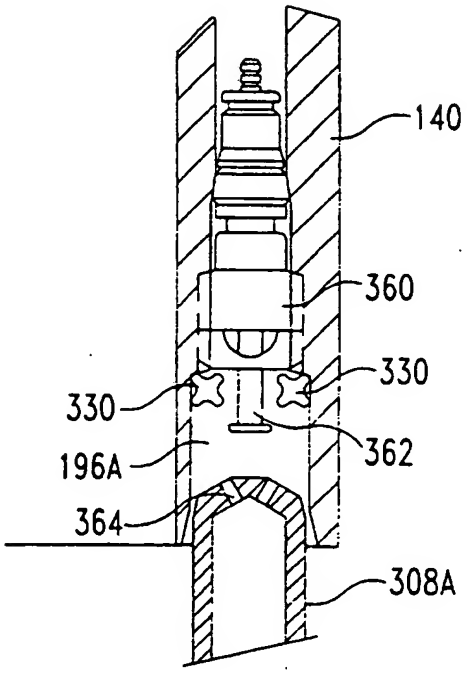

FIG. 16

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/05339

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : B01J 8/06; B01L 3/14
US CL : 422/196, 99, 102
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 422/196, 99, 102, 63, 101; 356/244, 246; 211/74

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS
search terms: septum, peptides, frit, filter, tube, funnel, block, synthesis, column, reactor

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US, A, 5,240,680 (ZUCKERMANN ET AL) 31 August 1993 (31.08.93), entire document.	1-42
Y	US, A, 4,398,382 (SUOVANIEMI ET AL) 16 August 1983 (16.08.83), entire document.	1-42
Y	US, A, 3,901,653 (JONES ET AL) 26 August 1975 (26.08.75), entire document.	6-13 and 27-36
Y, P	US, A, 5,419,874 (COASSIN ET AL) 30 May 1995 (30.05.95), entire document.	1-42
Y	US, A, 5,356,814 (CARRICO, JR. ET AL) 18 October 1994 (18.10.94), entire document.	1-42

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 JULY 1996	09 AUG 1996

Name and mailing address of the ISA/US	Authorized officer
Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	ALEXANDER MARKOFF
Facsimile No. (703) 305-3230	Telephone No. (703) 308-0651

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/05339

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US, A, 5,108,704 (BOWERS ET AL) 28 April 1992 (28.04.92), entire document.	1-121
Y	US, A, 5,039,493 (OPRANDY) 13 August 1991 (13.08.91), entire document.	43-121
Y	US, A, 5,283,039 (AYSTA) 01 February 1994 (01.02.94), entire document.	43-121
Y	US, A, 5,219,528 (CLARK) 15 June 1993 (15.06.93), entire document.	43-121
Y	US, A, 5,324,480 (SHUMATE ET AL) 23 June 1994 (23.06.94), entire document.	122-136
Y	US, A, 5,061,639 (LUNG ET AL) 29 October 1991 (29.10.91), entire document.	122-136
Y	US, A, 5,324,483 (CODY ET AL) 28 June 1994, (24.06.94), entire document.	

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/05339

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remarks on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☒ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/05339

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING

This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I,claims 1-121, drawn to a reaction chamber and a reaction block.

Group II,claims 122-124, drawn to a container rack.

Group III,claims 125-136, drawn to a docking station.

The inventions listed as Groups I, II and III do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The invention of Group I is a reaction block having a plurality of reaction chambers. The reaction block can be used for conducting chemical reactions. The reaction block does not require for it's use any container rack. The reaction block does not require the special technical features of the docking station and can be used alone.

The invention of Group II is a container rack for supporting a plurality of containers. The container rack is intended to be used in a pipetting station.

The invention of Group III is a docking station. The docking station does not require a reaction block having plurality of reaction chambers. Moreover, the docking station does not have any pipetting means and does not require any container or container rack.

The inventions are not so linked by a special technical features so as to form a single general inventive concept.